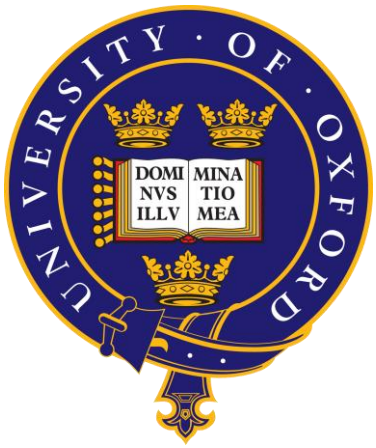
One-pot Nitro-Mannich Cascade Reactions:

New Methodologies and Synthetic Applications

A thesis submitted in partial fulfilment of the requirement for

the degree of Doctor of Philosophy (D. Phil.)



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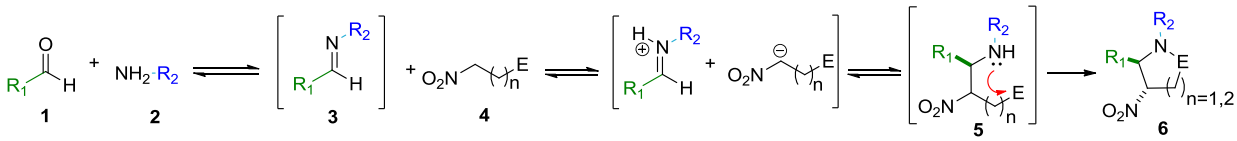
Nitro-Mannich Reaction Cascades: New Methods and Synthetic Aplications

Sophie M-C. Pelletier, Wadham college
DPhil. Organic chemistry, Michaelmas 2011

Piperidine and pyrrolidine rings are common motifs found in many biologically active natural products and drugs. Therefore, they have led to considerable interest from the synthetic community. Despite the many publications in the field, there is still no general method that can be routinely employed for the whole class of compounds. In addition, in the last 20 years, cascade sequences have become increasingly important as they are more time effective and "atom economical" than the traditional *one step – one vessel* approach. Accordingly, our work focuses on the development of new methodologies for the one-pot synthesis of pyrrolidine and piperidine heterocycles.

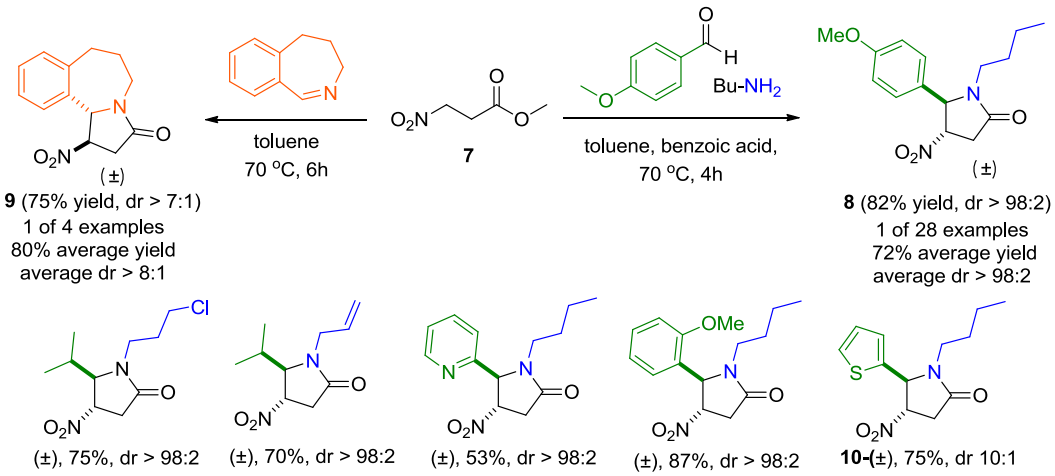
Building on previous studies within the Dixon group, cascade sequences involving an initial reversible nitro-Mannich reaction between a nitro-alkane **4** and an imine **3** followed by an irreversible cyclisation reaction of the amine functionality in the direct nitro-Mannich adduct **5** were studied (Scheme 1).



Scheme 1: Cascade sequences involving a nitro-Mannich reaction

Development of a nitro-Mannich / Lactamisation cascade for the synthesis of *trans* 1,5-disubstituted 4-nitropyrrolidinones

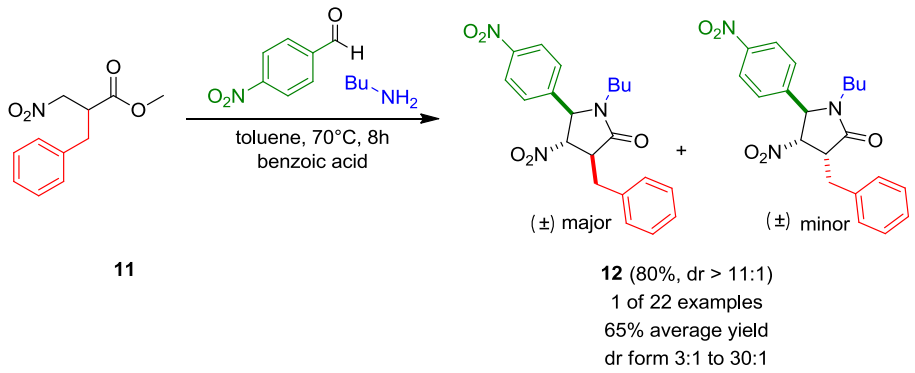
An efficient diastereoselective nitro-Mannich/lactamisation reaction cascade of methyl 3-nitropropanoate **7** with cyclic and acyclic imines for the direct preparation of monocyclic **8** and fused tricyclic **9** pyrrolidinone derivatives was developed (Scheme 2).[2] The reaction is easy to perform, broad in scope and tolerates a wide variety of functional groups (halides, alcohols, esters, ketals, etc). For the mono-cyclic methodology, 28 examples with a very good average yield of 72% and excellent diastereocontrol (typical dr >98:2) were obtained using optimized conditions and varying the amine and the aldehyde. The *trans* relationship of the major diastereoisomer was determined unambiguously by X-ray crystallography of **10**.



Scheme 2: Diastereoselective synthesis of monocyclic and fused tricyclic pyrrolidinones

A one-pot nitro-Mannich / Lactamisation cascade for the synthesis of 1,3,5-trisubstituted 4-nitropyrrolidinones

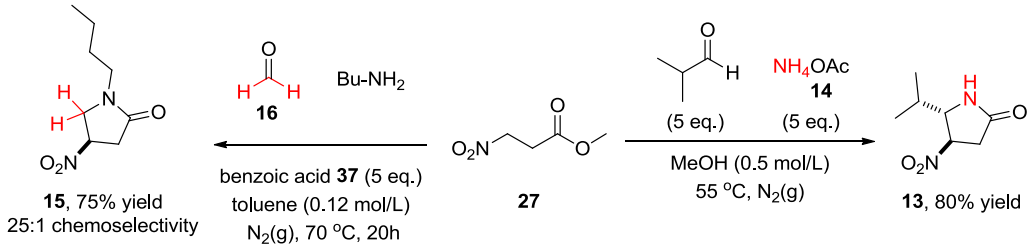
In order to access natural products and biologically active compounds containing pyrrolidine and pyrrolidinone rings substituted in the 3 position, the previously described methodology was extended to the synthesis of 1,3,5-trisubstituted 4-nitropyrrolidinone derivatives **12** using α-substituted 3-nitropropanoate **11**. Using a one-pot protocol, 15 derivatives were synthesised in good yields (65% average) and diastereomeric ratio ranging from 5:1 to 11:1 in favour of the *trans/trans* diastereoisomer (Scheme 3).[3] Several ^{1}H NMR studies were undertaken in order to test the influence of different variables on the diastereocontrol. It was found that the only factor which had a significant influence on the diastereomeric ratio was the steric hindrance of the different substituents. Another set of 7 compounds, with diastereomeric ratio ranging from 3:1 to 30:1, were specifically designed to exemplify the influence of the steric hindrance on the diastereocontrol.



Scheme 3: Diastereoselective synthesis of 1,3,5-trisubstituted 4-nitropyrrolidinones

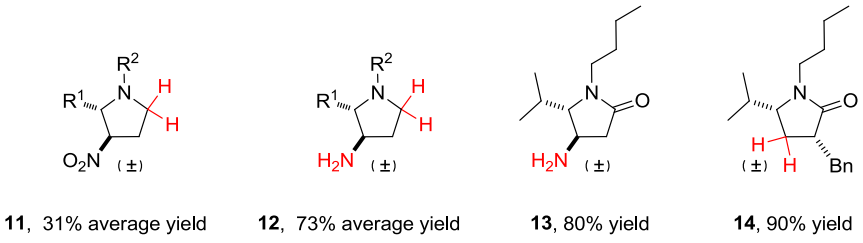
Extension of the methodologies and applications

The nitro-Mannich / lactamisation cascade of **7** was developed further to allow the rapid synthesis of 5-isopropyl-4-nitropyrrolidin-2-one **13** from reaction with ammonium acetate **14** and 1-butyl-4-nitropyrrolidin-2-one **15** from reaction with formaldehyde **16** (37% solution in water) (Scheme 4).



Scheme 4: Further extension of the nitro-Mannich / lactamisation cascade

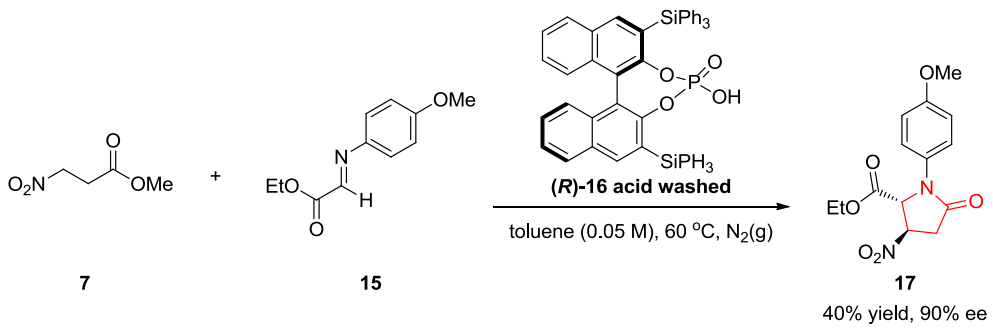
In addition, the synthetic utility of the nitro-pyrrolidinones formed was exemplified through various functional group modifications. The selective reduction of the lactam carbonyl was performed in the presence of the nitro group (product **11**), the reduction of the nitro group to the corresponding amine was achieved successfully in the presence (product **13**) or absence (product **12**) of the carbonyl group and the nitro group was successfully removed under radical conditions to form **14** (Scheme 5).



Scheme 5: Various functional group modifications

An enantioselective version of the nitro-Mannich / Lactamisation cascade

An enantioselective version of the nitro-Mannich / lactamisation cascade under chiral Brönsted acid catalysis has been studied thoroughly. The reactivity of the initial system had to be tuned in order to limit the background reaction and allow the catalytic reaction to take place. The results obtained after optimization of the reaction conditions are very promising (up to 90% ee on various substrates) (Scheme 6).



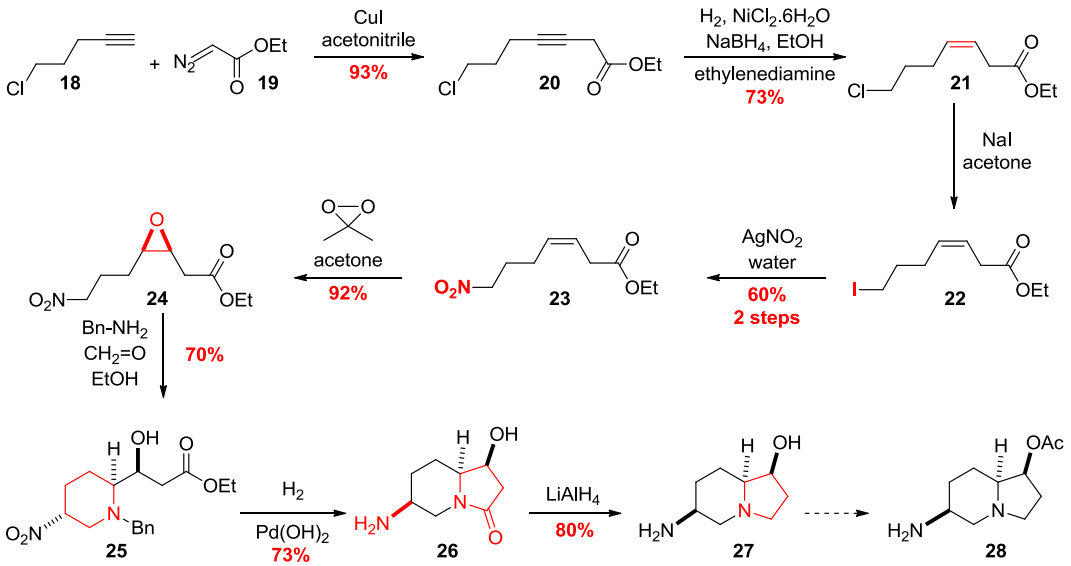
Scheme 6: Enantioselective nitro-Mannich / lactamisation cascade

Studies towards an understanding of the nitro-Mannich / Lactamisation cascade

Several ^{1}H NMR studies as well as Raman spectroscopy, UV spectropscopy and EPR (in the lab of Dr. Wesley Browne, Groningen University, The Netherlands) have been undertaken in order to better understand the nitro-Mannich / Lactamisation cascade reaction as well as the origin of the stereocontrol. For instance, these studies allowed us to understand the role of the oxygen in the reaction as well as to identify the rate determining step.

A formal synthesis of slaframine *via* a nitro-Mannich/ epoxide ring opening cascade

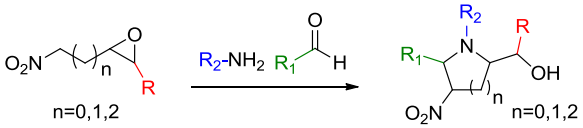
A formal synthesis of slaframine **28** was achieved in 8 steps and 15% overall yield from commercially available 5-chloropentyne **18** (Scheme 7). The copper catalyzed coupling of 5-chlororopent-1-yne **18** with diazoacetate **19** provided the alkyne **20** in 93% yield. After several optimization studies, using different metal sources, partial hydrogenation of the alkyne to the desired *Z*-alkene **21** was performed in 73% yield with nickel boride. A Finkelstein reaction followed by a nitration generated **23** in 60% over the two steps. Then, a *syn*-epoxidation with DMDO allowed the formation of the key intermediate **24** in 92% yield. After several attempts at forming **26** in a one-pot nitro-Mannich/ epoxide ring opening / lactamisation cascade, the 6 and 5-membered ring were constructed stepwise. A first nitro-Mannich / epoxide ring opening cascade, with benzylamine and formaldehyde, afforded the piperidine ring **25** in 70% yield. Then, a catalytic hydrogenation with palladium hydroxide allowed the cleavage of the benzyl group with subsequent lactamisation onto the ester to form the pyrrolidinone ring and the reduction of the nitro group to the amine with the desired stereochemistry in 73% yield. Finally, a $LiAlH_4$ reduction of the lactam carbonyl of **26** afforded **27** in 80% yield and provided a formal synthesis of slaframine **28** in 8 steps.



Scheme 7: A formal synthesis of slaframine 28 in 18% overall yield

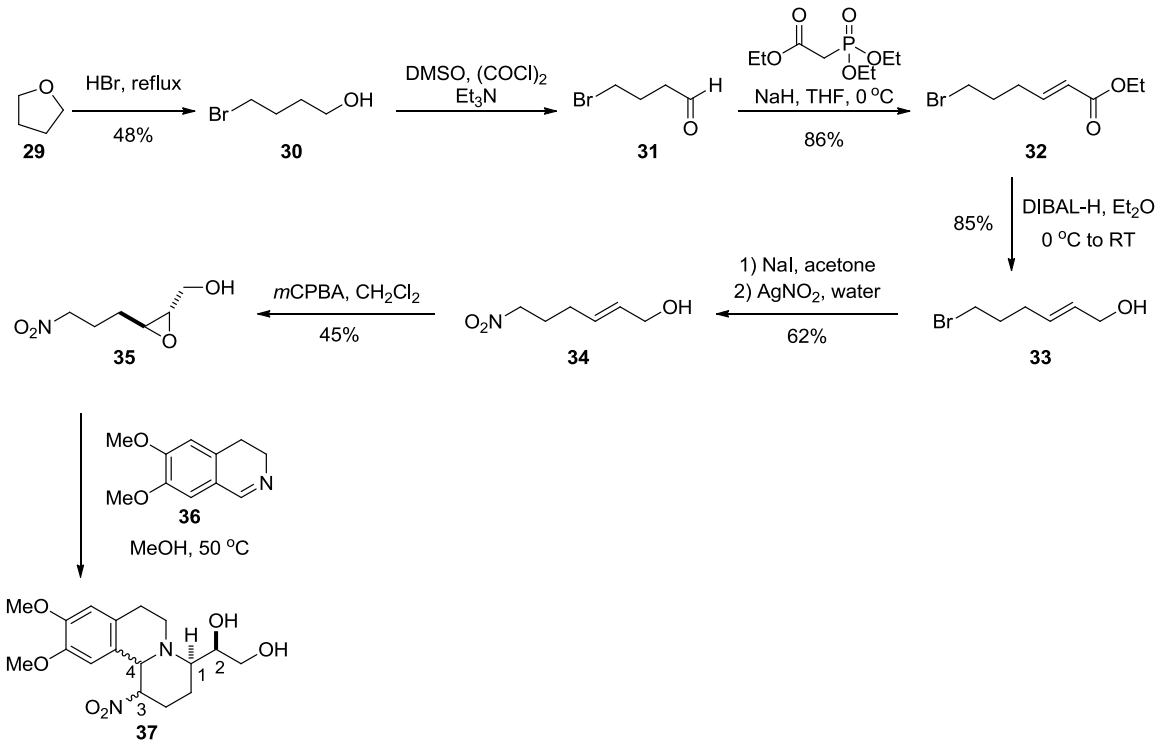
Development of a methodology towards a general nitro-Mannich / epoxide ring opening cascade for the synthesis of pyrrolidine and piperidine rings

Following on the proof of principle obtained in the synthesis of Slaframine, we decided to develop a new nitro-Mannich / epoxide ring opening to easily access pyrrolidine and piperidine rings (Scheme 8).



Scheme 8: General nitro-Mannich / epoxide ring opening cascade

A key intermediate to start developing the methodology has been synthesized in 6 steps from tetrahydrofuran **29** (Scheme 9). Opening of tetrahydrofuran **29** with HBr followed by a Swern oxidation of the primary alcohol **30** and a HWE reaction afforded the α,β-unsaturated ester **32** in 39% yield. The allylic alcohol **33** was obtained *via* a reduction with DIBAL-H in 85% yield. A Finkelstein reaction followed by a nitration with silver nitrite allowed the formation of the intermediate **34**, which was subsequently oxidized by DMDO to access the key epoxide **35**. Finally, **37** was successfully isolated as the products of a nitro-Mannich / epoxide ring opening cascade, leading the way to the development of a new methodology (Scheme 9).



Scheme 9: Synthesis of the key epoxide 35 and proof of principle of a nitro-Mannich / epoxide opening cascade

Conclusion:

A new nitro-Mannich / Lactamisation cascade was developed for the one pot synthesis of *trans* 1,3-substituted 4-nitropyrrolidinones in high chemical yield. The methodology has been extended to the synthesis of fused tricyclic pyrrolidinones and 1,3,5-substituted 4-nitropyrrolidinones in very good yields and an enantioselective version of the cascade is under development. Further manipulation of the products was demonstrated (including the reduction of the nitro group and/or the carbonyl group and denitrohydrogenation). In addition, a formal synthesis of *rac*-Slaframine was successfully achieved using a nitro-Mannich/epoxide opening cascade and a general methodology using such a cascade for the synthesis of pyrrolidine and piperidine rings is being developed. Finally, several mechanistic studies were undertaken to rationalize the results generated.

Acknowledgements

I could not have gone through my PhD the way I did if it was not for all the people around me and I would like to take the opportunity to thank everyone of them.

First, I would like to thank Darren for giving me the opportunity to join his research group and for the exiting chemistry he enabled me to perform. A PhD brings its share of though time so I would like to thank you for always having your office door open for advice and valuable inputs. I learnt a lot having you has my Professor and I am really grateful for it.

A great thant you to Peter Ray, my industrial supervisor, for his guidance throughout my PhD and especially during my case award placement at Newhouse. Thank you also for the nice Sunday hikes with Jane and Francesca! I am not forgetting all the people of lab 1123 in Newhouse: Anna, Kate, Steven, Jorgen, Julia and Helen. I had a great time with you guys and I really enjoyed learning all the funny scottish words!

What would be a PhD thesis without labmates? Merci tout particulièrement à Ben (Ben Ben Ben) et Isabelle à qui je dois d'avoir garder ma santé mentale (enfin à quelques craquages près!). Sans vous, nos petites soirées et les parties de «tout le monde veut prendre sa place» je n'aurai pas tenu le coup! Ben, c'est promis je ne ferai plus dépasser les conditions de la réaction des flèches!! Isabelle, je veillerai toujours à ce que mes molécules soient bien centrées! Car en plus d'être devenus mes amis vous avez été des mentors qui m'ont beaucoup appris! Encore merci à tous les deux!

Merci aussi à Michael qui m'a beaucoup guidé et appris dans mes deux premières années de thèses. Je n'oublierai pas nos week-end rires et chansons et nos soirées disco dans le labo!

Thank to Wolfgang for helping me in my first months as a PhD student (you are truly better than Scifinder!) and Pavol for his help and advice througout my PhD: you have been of really great help.

Thank to all the group members past and present, G5 and G6: Tom, Chloe, Kath (the haribo and the unspoken cold war for music), Meiling, Filipo, Andrew, Ali for your good mood and the nice atmosphere you held in the lab (I blame it on the Boogie!! lol), Matt (even though it was short, we always enjoyed you crazy drunken week-end stories), Dave, Eddy, Ben B. (I definitely learnt a lot with you!), Iacovos (thanks for the salsa evenings!), Marta (and the crazy times), Lei, Swarup, Alex, Kaily, Alistair (Oui Sophie!), Chris and Rob.

Bueno, no voy a olvidar a los espagnoles (y Mexivano y cubano! Jaja!): gracias a vosotros el tiempo en el laboratorio fue mucho mas agradable. Gracias a Bea (mi companera y amiga de primer ano, por la manana en ingles y la tarde en espano, y tu tortilla de patata que me encanta), Irene (muchas gracias por tu amistad y todos los mementos juntas in Oxford, Cambridge y espero en Madrid y Suisa), Orlando (Cubanito, estoy muy enfadada que no has venido mas pronto en el grupo! Me he encantado estar tu vecina de laboratorio y companera de salsa!), Rogelio y Lucia (que buen tiempos hemos pasado este verano!) y los otros del Spanish gang (Camilio, Mercedes, ...).

Une pensée particulière pour le groupe des français: Marie-Caroline (MC), Cédric, Michael, Eric, Ben et Alex, Isa et Bouboune, sans oublier Ludo (mon colloc préféré) pour nos soirées “bonne bouffe et jeux de société!” Je n’oublierai pas de si tôt nos parties endiablées de UNO!

I would also like to thank the NMR team: Barbara, Tina and Tim and the teaching lab crew: Malcolm, Alan and Lydia, who have been of great help and very nice company during my PhD!

I am not forgetting that I did not do a PhD by chance and I can’t tell how grateful I am to have had Chris VanDeusen and René Lacrois as my supervisors during my internships. Chris, I want to thank you for the daily chemistry problem you draw on your board for me and the long hours you spent teaching me in the lab in Bridgewater. René, thanks to you I grew from a chemistry student to an almost independent chemist! I will never forget our adventure to France for my master’s defense! I would like to address a special thank you to Dave B. (my adoptive American dad, alias Tonton canasson!) for all the guidance and help through my studies! Thanks to Dave Aldous for the help to find my way to Oxford and the valuable talks about my professional choices.

Je voudrai addresser un remerciement tout particulier à Pierre-Emmanuel, l'éditeur en chef de ce manuscript pour m'avoir supporter et m'avoir preparer de bons petits plats pendant toute ma redaction :D!

Je voudrai maintenant remercier ma famille et mes amis qui m'ont encouragé et soutenu depuis de longues années! Merci Maman, Papa, Antoine, Tonton et Marraine pour votre soutien et vos encouragements sans faille, je n'y serai pas arrive sans vous! Je tiens à rappeler que pendant les concours de prépas Tonton m'appelait le matin pour me souhaiter bonne chance, le midi pour savoir comment ça c'était passé et m'encourager pour l'après midi, et le soir pour avoir les impressions de la journée! Et cela pendant 3 semaines! Je n'oublie pas Mémé et Pépé, qui auraient été très fiers de venir voir leur petite fille recevoir son diplome à Oxford et Granny qui m'a bien aide pendant les études. Merci à Nicole et aux soirées au bord de ta cheminée, à Gilles T. pour les conseils en chimie et surtout à Delphine pour les coups de fils et les e-mails multi-journaliers et notre complicité depuis CPE.

Cette thèse est dédiée à ma famille et à mes amis

Avec une pensée particulière pour ceux qui nous ont quitté trop tôt

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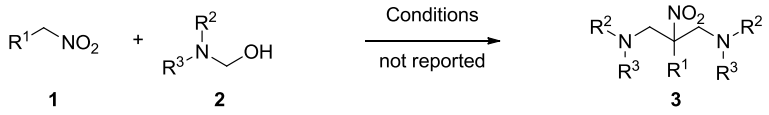
Introduction

I.1 The nitro-Mannich reaction

The nitro-Mannich reaction (or aza-Henry), discovered in 1897 by Louis Henry, is the nucleophilic addition of nitroalkanes to imines to form β-nitroamine derivatives.[1] It is a variant to the Mannich and the Henry reactions, which constitutes, with the aldol reactions, some of the most common processes to form C-C bond *via* the addition of a carbon nucleophile to a C=X (X = O, N, S) double bond. Whereas those three reactions (Henry, Mannich and aldol) have been studied extensively, the nitro-Mannich has received very little interest from the synthetic community throughout the 20th century. Most of the early publications describing the nitro-Mannich reaction were of limited scope and of poor yield and diastereocontrol. However, since the late nineties, there have been an increasing number of publications in the field and several diastereselective and enantioselective methodologies have been developed. The products formed are versatile and they can easily be transformed *via* various functional group modifications. Indeed, the nitro-Mannich reaction is starting to appear in syntheses of natural products or biologically active compounds.

I.1.1 Discovery and early work

The first nitro-Mannich reaction[1] was reported by Henry in 1897, the year following his publication of the first nitroaldol reaction, later renamed the Henry reaction.[2] Henry described the reaction of nitroalkanes **1** with hemi-aminals **2** to give β-nitrodiamines **3** (Scheme 1).



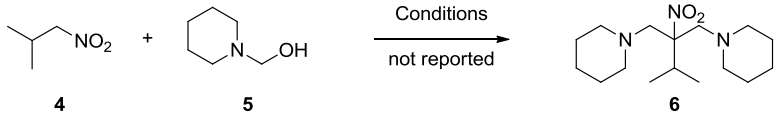
1 **2** **3**

Scheme 1 – The first reported nitro-Mannich reaction by Henry

Presumably, loss of water from **2** gives an iminium ion that is subsequently attacked by nitroalkane **1** to form an intermediate nitro-Mannich β-nitroamine product, which in turn, can react with a second equivalent of iminium ion to give rise to the product β-nitrodiamines **3**.

[1] (a) Henry, L. *Bull. Acad. Roy. Belg.* **1897**, *33*, 412. (b) Henry, L. *Ber.* **1905**, *33*, 2027.
[2] Henry, L. *Compt. Rend. Hebd. Seances Acad. Sci.* **1896**, *120*, 1265.

In 1901, Mousset published a similar reaction towards β-nitrodiamines **6** from the reaction of 2-methyl-1-nitropropane **4** with hemi-aminal **5** (Scheme 2).[3]



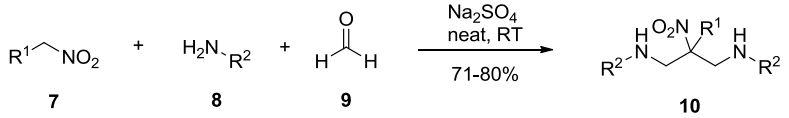
4 **5** **6**

Scheme 2 – Nitro-Mannich reaction reported by Mousset

A few years later, Duden, Bock and Reid repeated Henry's synthesis of 2-nitro-1,3-bisdimethylaminopropane and further reduced the nitro group to the corresponding amine using $SnCl_2$.[4] However, they were unable to reproduce the reaction of nitromethane with *N*-hydroxymethylamine. Except for Cerf's[5] work, there were no further advances on the nitro-Mannich reaction until extensive studies were published independently by Johnson and Senkus in 1946.

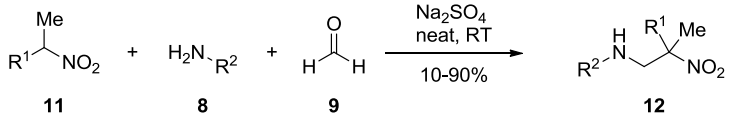
Senkus described the reaction of mono- **7** and disubstituted nitroalkanes **11** respectively with primary amines **8** and formaldehyde **9**.[6] The reaction was performed under neat conditions and in the presence of Na_2SO_4. β-Nitrodiamines **10** and β-nitroamine **12** were obtained in 71-80% and 10-90% yield respectively (Scheme 3). The author believed that amines **8** and formaldehyde **9** formed the corresponding hemi-aminals *in situ* before reacting with nitroalkanes **7** and **11**, presumably *via* the iminium ion. Products **10** and **12** were also synthesised by reacting amines **8** with the Henry product of the reaction of nitroalkanes **7** and formaldehyde **9**.

[3] Mousset, T. *Bull. Acad. Roy. Belg.* **1901**, 622.
[4] Duden, P.; Bock, K.; Reid, H. J. *Ber.* **1905**, *33*, 2036.
[5] (a) Cerf de Mauny, H. *Bull. Soc. Chim.* 1**931**, *4*, 1451;(b) Cerf de Mauny, H. *Bull. Soc. Chim.* **1931**, *4*, 1460.
[6] Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10.



7 8 9 10

R^1= Me, Et, Cl; R^2= ^{i}Pr, Bn

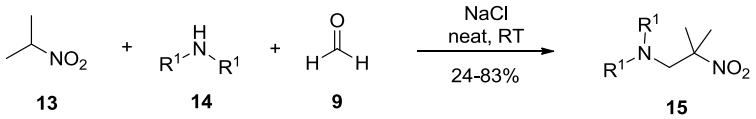


11 8 9 12

R^1 = Me, Et; R^2 = Me, ^{i}Pr, ^{n}Bu, Bn, 1-methylpropyl, 1-phenylethyl, $CH(Me)CH_2OH$, $C(Me)_2CH_2OH$, $CH(Et)CH_2OH$

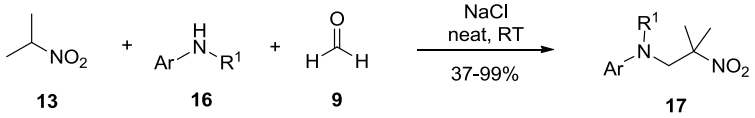
Scheme 3 – Nitro-Mannich reaction reported by Senkus

Johnson reported two new advancements of the nitro-Mannich reaction involving primary, secondary or aromatic amines (Scheme 4).[7,8] β-nitroamines and β-nitrodiamines **15** or **17** were synthesised either in one-pot (where formaldehyde **9**, nitroalkane **13** and amines **14** or **16** were mixed simultaneously) or in two steps (amines **14** or **16** would be added to the Henry product of the reaction of formaldehyde **9** with nitroalkane **13**). In the latter, the nitro-alcohol was believed to first "decompose into nitroparaffin and formaldehyde *via* a retro-Henry reaction", thus requiring longer reaction times.



13 14 9 15

R^1 = Me, ^{n}Bu, CH(Et)pentyl; cyclic amines: morpholine, piperidines, 2,5-dimethylpyrrolidine.



13 16 9 17

R^1 = H, Me, ^{n}Bu

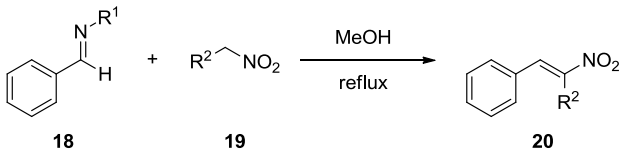
Scheme 4 – Nitro-Mannich reaction with secondary amines

In addition, Senkus and Johnson, both reported the reduction of the nitro group of the β-nitrodiamines **10** and β-nitroamines **12**, **15** and **17** to the corresponding amines with Raney nickel.

In 1943, Hass and Riley described the first nitro-Mannich reaction between a preformed imines **18** and nitroalkanes **19** (Scheme 5).[9] Nitro-olefins **20** were obtained instead of the expected β-

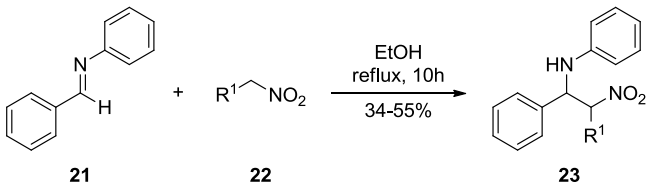
[7] Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 14.
[8] Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12.
[9] Haas, H.; Riley, E. *Chem. Rev.* **1943**, *33*, 409.

nitroamines. Since the reaction was heated to reflux overnight it is reasonable that elimination to the conjugated system **20** occured under thermodynamic control.



Scheme 5 – Synthesis of a nitro-olefin from a Nitro-Mannich reaction

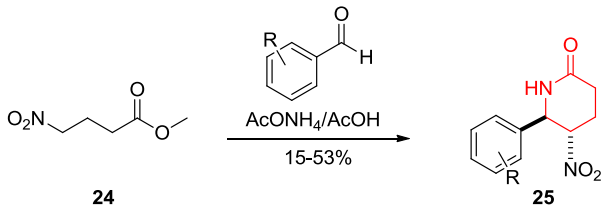
Interestingly, Hurd and Strong reported the synthesis of β-nitroamine **23** from the reaction of nitroalkanes **22** with the preformed imine **21** derived from aniline (Scheme 6).[10]



R^1 = Me, Et

Scheme 6 – Nitro-Mannich reaction with a preformed imine

The next major development of the nitro-Mannich reaction came in 1976 when Muhlstadt[11] and Jain[12] independently reported a reaction cascade, involving an initial nitro-Mannich reaction between a nitroalkane and an imine, followed by an irreversible lactamisation. They both described the reaction between methyl 4-nitrobutanoate **24**, an aromatic aldehyde and ammonium acetate to form the corresponding piperidinone **25** (Scheme 7). Through ^{1}H NMR analysis, Jain confirmed the *trans* stereochemistry of nitropiperidinones **25**.



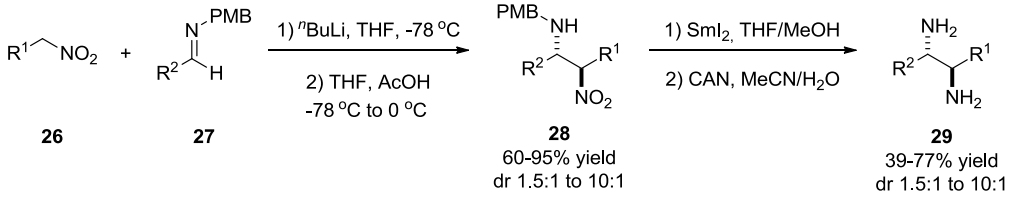
R = Me, OMe, Cl, $N(Me)_2$, CN, NO_2, Br

Scheme 7 - First nitro-Mannich / lactamisation cascades

In both publications, the scope of the reaction was fairly limited, and included only a small number of substituted aromatic aldehydes.

[10] Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813.
[11] Mühlstädt, M.; Schulze, B. *J. F. Prakt. Chem.* **1975**, 919.
[12] Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, *615*.

The first acyclic diastereoselective nitro-Mannich reaction was reported by Anderson and co-workers in 1998 (Scheme 8).[13] They described the addition of lithium salts of nitroalkanes **26** to *N*-(p-methoxybenzyl) imines **27** in the presence of acetic acid in good to excellent yields (60 to 95%) and good diastereocontrol (1.5:1 to 10:1 in favour of the *anti* diastereoisomer). β-Nitroamines **28** were further reduced and deprotected to the more stable diamines **29** without erosion of the diastereomeric ratio. The mild reaction conditions could tolerate aromatic, branched aliphatic and enolisable imines.



26 **27** **28** 60-95% yield dr 1.5:1 to 10:1 **29** 39-77% yield dr 1.5:1 to 10:1

R^1 = Me, Et, Ph; R^2 = Ph, ^{n}Pn, ^{c}Hex, Ph, CH_2OBn, $(CH_2)_3Ph$

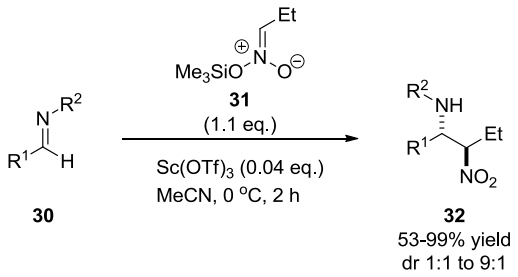
Scheme 8 – First Acyclic diastereoselective nitro-Mannich reaction

This work represents a milestone in the research around the Nitro-Mannich reaction, as from then on, an increasing interest for this reaction can be witnessed, with over 150 reports covering both diastereoselective and/or enantioselective versions of the reaction using metal-catalyst (section I-1-2) or organocatalysts (section I-1-3).

I.1.2 Stereoselective metal-catalysed nitro-Mannich reaction[14]

With the aim of improving the efficiency of their reaction and of developing an enantioselective version of it, Anderson *et al.* reported in 2001 the reaction of aryl and alkyl imines **30** with 1-trimethyl nitropropanoate **31** catalysed by scandium triflate (Scheme 9).[15]

[13] Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.
[14] For a review: a) Westermann, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 151. b) Marqués-lópez, E. ; Merino, P. ; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, *15*, 2401.
[15] Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, *6*, 850.

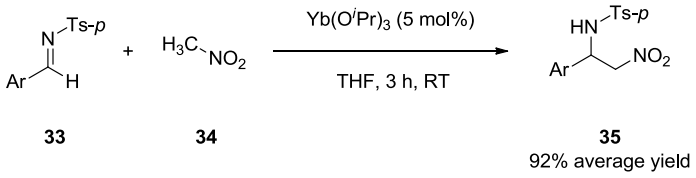


R^1 = Ph, *c*-hexyl, $(CH_2)_4CH_3$, $(CH_2)_4Ph$, 2-furyl; R^2 = PMB, PMP

Scheme 9 – Synthesis of β-nitroamines 30

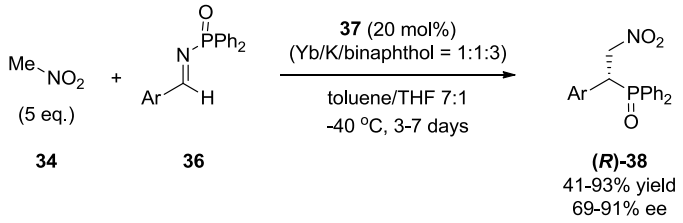
The desired β-nitroamines **32** were isolated in moderate to excellent yields (53% to 99%) and no to good diastereoselectivities (1:1 to 9:1). In most cases, the PMP protected imine was found to provide higher yields and diastereocontrol than the PMB analog.

The same year, Qian *et al.* also reported the use of lanthanides derivatives as catalyst of the nitro-Mannich reaction between aryl sulfonylimines **33** and nitromethane **34** in excellent yields (92% average yield) (Scheme 10).[16]



Scheme 10 – Nitro-Mannich reaction of sulfonylimines catalysed by $Yb(O^iPr)_3$

The first catalytic enantioselective nitro-Mannich reaction was achieved by Shibasaki's group in 1999 between nitromethane **34** and *N*-phosphinoyl imines **36** (Scheme 11).[17]



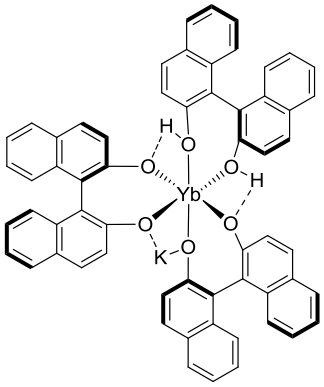
Ar = Ph, 4-Cl-C_6H_4, *p*-tolyl, 2-furyl, 2-thiophenyl

Scheme 11 – First enantioselective nitro-Mannich reaction by Shibasaki

The authors reported the use of heterobimetallic complex containing both Brønsted basic and Lewis acidic functionalities. They investigated several catalytic systems, with different metals and various

[16] Qian, C.; Gao, F.; Chen, R. *Tetrahedron Letters* **2001**, *42*, 4673.
[17] Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

stoichiometric ratios, and they found that the complex [YbK(binaphthoxide)$_3$] **37** (Figure 1), prepared from a mixture of Yb(O^{i}Pr)$_3$, KOtBu and (*R*)-binaphtol in a 1:1:3 ratio, was the best heterobimetallic catalyst for the reaction.



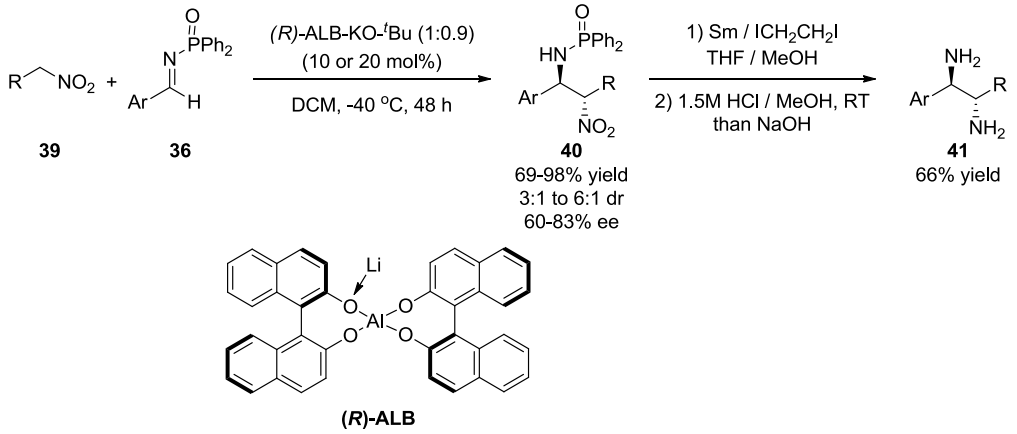
37

Figure 1 **– Heterobimetallic complex (Yb/K/(*R*)-naphthol 1/1/3) 37**

The scope of the reaction was limited to the reaction of aromatic *N*-phosphinoyl imines **36** with nitromethane **34** but the products **38** were isolated in moderate to excellent yields (41% to 93%) and with good to excellent enantioselectivity (69% to 91% ee). Unfortunately, other nitroalkanes, such as nitroethane, failed to react under the reaction conditions. In addition, the reaction required long reaction times (3 to 7 days) at cryogenic temperatures and with slow addition of nitromethane **34** over 27 hours.

In an extension of this work, Shibasaki and co-workers published in 2001 the first diastereoselective catalytic asymmetric nitro-Mannich reaction with nitroalkanes **39** and *N*-phosphinoyl imines **36** (Scheme 12).[18] The reaction was catalysed by Al-Li[(*R*)-binaphthoxide]$_2$ (ALB) KO-*t*-Bu complex, a heterobimetallic asymmetric complex containing both Brønsted acid and Lewis acidic functionalities.

[18] Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980.



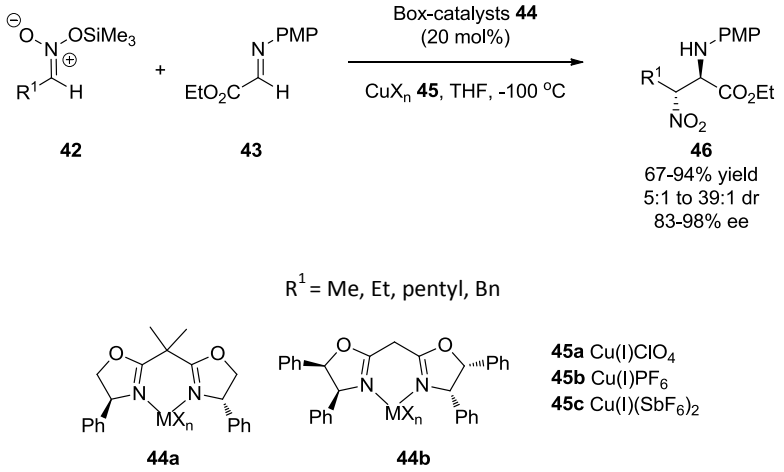
R = Me, Et, $(CH_2)_2OBn$; Ar = Ph, 4-Cl-C_6H_4, 4-MeO-C_6H_4.

Scheme 12 – First diastereoselective catalytic asymmetric nitro-Mannich reaction

The *anti* nitro-Mannich products **40** were obtained in moderate to very good enantioselectivities (60% to 83% ee) and low to moderate diastereoselectivities (3:1 to 6:1 dr). The scope of the reaction with respect to the nitroalkane **39** was extended from the exclusive use of nitromethane **34** to nitroethane and 1-benzyloxy-3-nitropropane. However, the scope of the reaction with respect to the imine was still limited to aromatic imines **36**.

In 2001, Jørgensen and co-workers published the first catalytic nitro-Mannich reaction that was both highly *anti* diastereoselective and enantioselective[19]. They described the reaction of silylnitronates **42** and PMP-protected iminoester **43** in the presence of 20 mol% of various copper-bisoxazoline catalysts (Scheme 13).

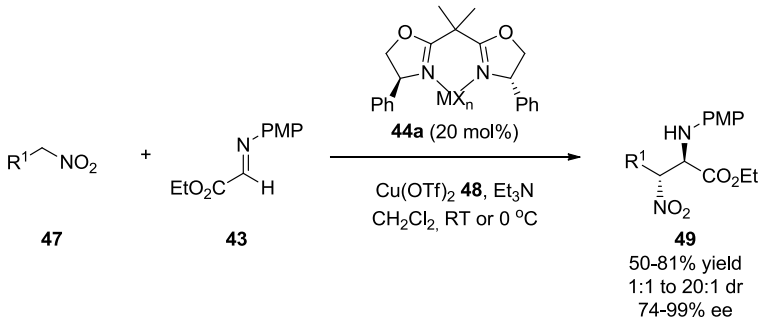
[19] Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.



Scheme 13 – Asymmetric nitro-Mannich reaction between silylnitronates 42 and imine 43

The use of silylnitronates **42** avoided the need for a base and *anti* β-nitro-α-aminoesters **46** were synthesised in very good diastereomeric ratios (up to 39:1) and excellent enantioselectivities (up to 97% ee). The scope of the reaction was also much wider than previous works.

The same year, the Danish group also presented the reaction of nitroalkanes **47** with iminoester **43** catalysed by bisoxazoline ligand **44a** (20 mol%) and copper (II) triflate **48** in the presence of triethylamine (Scheme 14).[20]

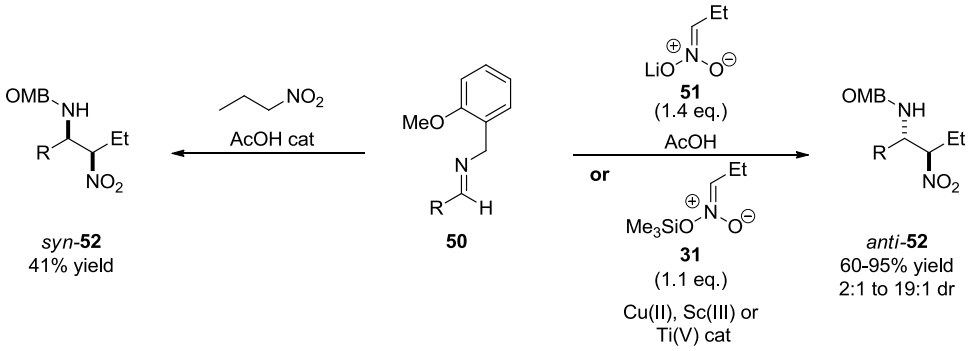


Scheme 14 – Asymmetric nitro-Mannich reaction between nitroalkanes 47 and imine 43

The reaction conditions are milder and the desired β-nitro-α-aminoesters **49** were formed in moderate to good diastereomeric ratios ranging from 1:1 to 19:1 and in excellent enantiomeric excesses up to 99%. It is noteworthy that imine **43** seems particularly well matched for enantioselective nitro-Mannich reactions.

[20] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.

In 2005, Anderson's group reported two new advancements of the nitro-Mannich reaction: a diastereoselective method and an asymmetric one. In the first article,[21] they describe the reaction of heteroaromatic or aliphatic *o*-methoxybenzyl protected imines **50** with lithium nitropropanate **51** in the presence of catalytic acetic acid (method A) or with trimethylsilyl nitropropanate **31** catalysed by Lewis acid $Sc(OTf)_3$, $Cu(OTf)_2$ or $Ti(O^iPr)$ (method B) to form *anti* β-nitroamines **52** (Scheme 15).



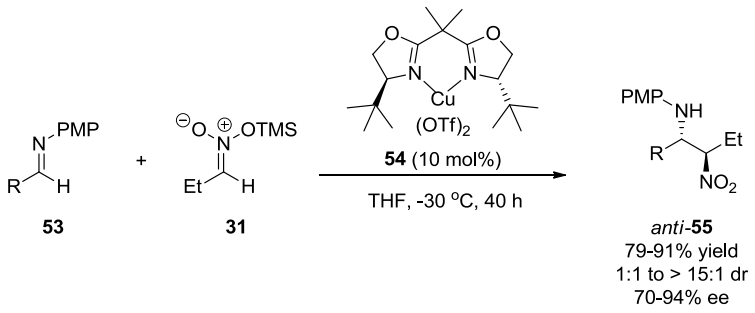
R = Ph, *n*-hexyl, 2-furyl, 2-thiophenyl, *n*-(N-methyl)pyrrole, ^{i}Pr, Me_2

Scheme 15 – Synthesis of *syn* and *anti* β-nitroamines 52

Both methods provided the product *anti*-**52** in excellent yields (85% in average) and in moderate to good diastereoselectivity (1:1 to 19:1 dr), but method A generally provided the highest degree of diastereocontrol. The products of the SmI_2 reduction of **52** to the corresponding diamines were subsequently reacted with phosgene to form cyclic ureas, and the OMB protecting group was successfully cleaved in refluxing neat TFA. In addition, they showed that the reaction of imine **50** with acetic acid in neat nitropropane allowed the selective synthesis of *syn*-**52**.

In the second article, Anderson *et al.* presented a general and efficient catalytic asymmetric nitro-Mannich reaction for the synthesis of *anti* β-nitroamines **55** (Scheme 16).[22] The addition of trimethylsilyl nitropropanate **31** to alkyl, aryl and heterocyclic PMP-protected imines **53** was catalysed by the chiral ^{t}Bu-BOX Cu(II) complex **54**. The reaction is broad in scope and uses low catalyst loading. The desired products **55** were isolated in excellent yields (86% in average) with low to very good diastereomeric ratio (1:1 to > 15:1) and good to excellent enantiomeric excess (70% to 94%).

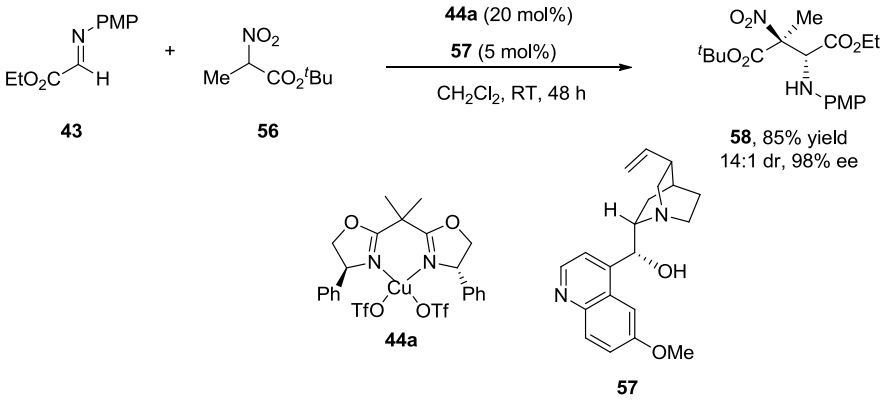
[21] Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.
[22] Anderson, J. C.; Howell, G. P.; Lawrence, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 5665.



R = Ph, *n*-pentyl, *c*-hexyl, 2-furyl, 2-CN-C_6H_4, 4-CN-C_6H_4, 2, 2-Cl-C_6H_4, 4-Cl-C_6H_4

Scheme 16 – Enantioselective synthesis of *anti*-55 bearing alkyl, aryl and heteroaromatic substituents

The same year, Jørgensen and co-workers reported a novel nitro-Mannich methodology to form quaternary stereocenters (Scheme 17).[23] 2-Nitropropanoic acid ^{t}butyl ester **56** was reacted with PMP-protected iminoester **43** in the presence of cinchona alkaloid **57** and chiral BOX Lewis acid complex **44a**. With as little as 5 mol% of catalyst **57**, the desired product **58** was isolated in a very good yield (85%), with a very good diastereomeric ratio (14:1) and an excellent enantiomeric excess (98%). However, the scope of the reaction was limited to the sole example of the reaction between iminoester **43** and nitropropanoic acid **56**.

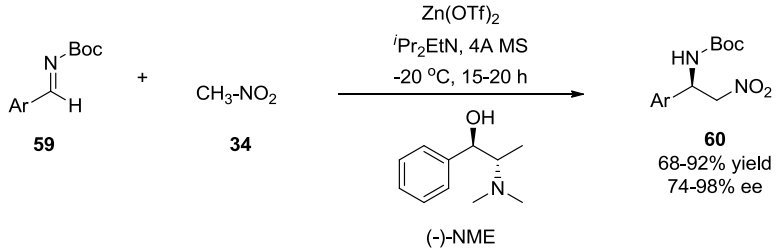


Scheme 17 – Formation of optically active quaternary centres in nitro-Mannich reactions

Palomo *et al.* described in 2006 the enantioselective nitro-Mannich reaction between Boc-protected aryl imines **59** and nitromethane **34** catalyzed by $Zn(OTf)_2$ (30%), Hünig's base (30%) and (-)-*N*-methylephedrine ((-)-NME, 45%) (Scheme 18).[24] The reaction tolerates aromatic imines bearing electron rich, electron-neutral and electron-poor substituents and the desired β-nitroamines **60** were

[23] Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.
[24] Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117.

isolated in good to excellent yields (68% to 92%) and excellent enantiomeric excess (92% ee in average).

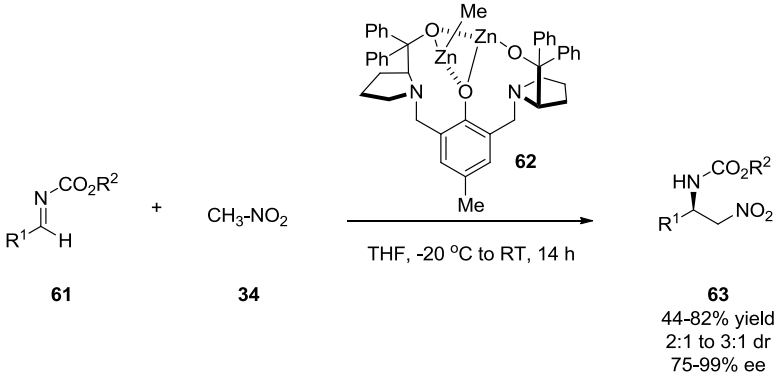


Ar = Ph, 1-naphthyl, 2-naphthyl, 2-Me-C_6H_4, 4-Me-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F_3C-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 3,5-Cl_2, 4-MeO-C_6H_2.

Scheme 18 – Enantioselective nitro-Mannich reaction catalysed by $Zn(OTf)_2$ and NME

The reaction was found to be sensitive to moisture and protic contaminants, and therefore the use of molecular sieves in the reaction was found to be crucial for the enantioselectivity.

In 2007, Trost *et al.* published the first enantioselective nitro-Mannich reaction of α,β-unsaturated imines catalysed by the dinuclear zinc catalyst **62** (Scheme 19).[25] The reaction scope was very broad and tolerated various imines **61** bearing aromatic and alkyl substituents as well as α,β-unsaturated ones. The desired products **63** were formed in moderate yields (56% in average) but with very good to excellent enantiomeric excess (75% to 99%).



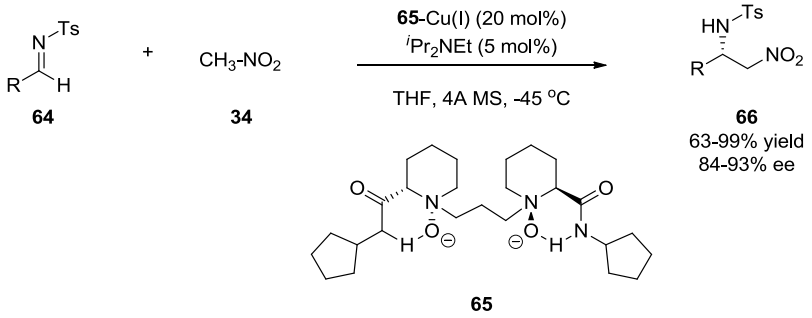
R^1 = ^{t}Butyl, $TBSOCH_2(CH_3)_2C$-, Ph, 2-furan, 2-thiophene, 2-Me-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, PhCH=CH;
R^2 = ^{t}Butyl, Bn, Me

Scheme 19 – Enantioselective nitro-Mannich reaction catalysed by dinuclear zinc catalyst 62

The same year, Feng and co-workers found that the nitro-Mannich reaction between *N*-tosyl imines **64** and nitromethane **34** could be catalyzed by the complex formed between *N*,*N*-dioxide **65** and copper(I) triflate (Scheme 20).[26] The scope of the reaction was probed with aromatic and heteroaromatic imines **64** bearing electron-donating, electron-withdrawing and electron-neutral

[25] Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.
[26] Zhou, H.; Peng, D.; Qin, B.; Hou, Z.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 10302.

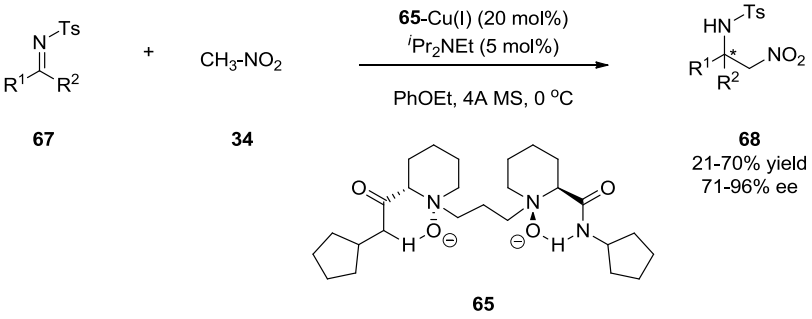
substituents around the ring. The corresponding β-nitroamines **66** were formed in excellent yield (83% in average) and with excellent enantioselectivities (89% in average).



R = Ph, 1-naphthyl, 2-naphthyl, 4-Me-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, 4-MeO-C_6H_4, 2-furyl, 4-Cl-C_6H_4.

Scheme 20 – Enantioselective nitro-Mannich reaction catalysed by N,N-dioxide 65

In addition, the following year, they extended the use of *N*,*N*-dioxide **65** and they reported the first enantioselective nitro-Mannich reaction of ketoimines **67** to form β-nitroamines **68** bearing a quaternary center (Scheme 21).[27] The desired products **68** were isolated in moderate yield (45% in average) but excellent enantiomeric excess (88% in average). In addition the scope of the reaction was broad and even included the imine of a dialkyl ketone.



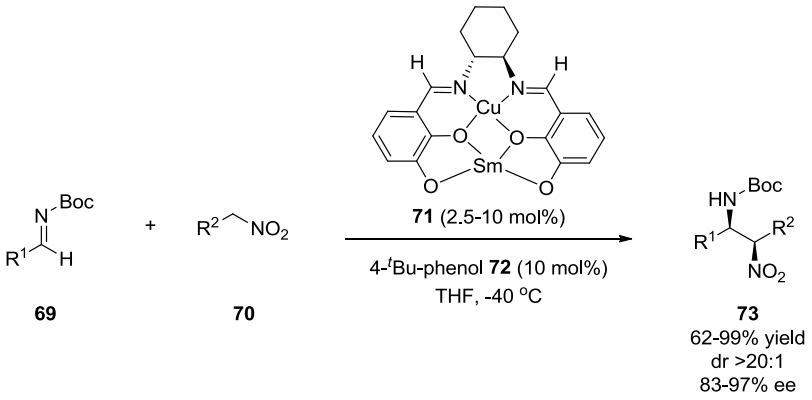
R^1 = Ph, 2-naphthyl, 2-furyl, 2-thienyl, cyclohexyl, $Ph(CH_2)_2$, 2-F-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 2-MeO-C_6H_4, 3-MeO-C_6H_4; R^2 = Me, Et.

Scheme 21 – First enantioselective nitro-Mannich reaction of ketoimines 67

In 2007, Shibasaki's group reported the first *syn*-selective asymmetric nitro-Mannich reaction (Scheme 22).[28] A heterobimetallic Cu/Sm/Schiff base (1:1:1) complex **71** was shown to catalyse the addition of nitroalkanes **70** to *N*-Boc-protected imines **69** in good to excellent yield (62% to 99%),

[27] Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305.
[28] a) For the communication: Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. b) For the full paper: Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925.

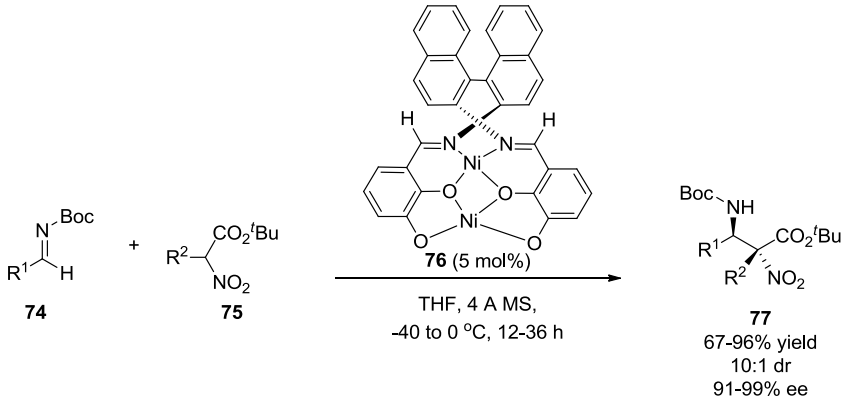
excellent enantiomeric excess (93% in average) and very high diastereoselectivity (> 20:1). Both Cu and Sm metal proved to be crucial to impart high *syn*-selectivity.



R^1 = Ph, 3-thienyl, ^{n}butyl, ^{i}butyl, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4;
R^2 = Me, Et, ^{n}propyl, Bn

Scheme 22 – First syn selective asymmetric nitro-Mannich reaction

In 2008, they showed the utility of the homodinuclear Ni_2-Shiff base **76** in the catalytic asymmetric nitro-Mannich reaction of ^{t}butylnitroacetates **75** and *N*-Boc imines **74** (Scheme 23).[29] α-Quaternary *anti*-α-nitro-β-amino esters **77** were obtained in good to excellent yield (67% to 96%), very good *anti*-diastereoselectivity (10:1 in average) and excellent enantioselectivity (91-99% ee). In addition, this newly developed catalyst is bench stable and the scope of the reaction was quite broad.

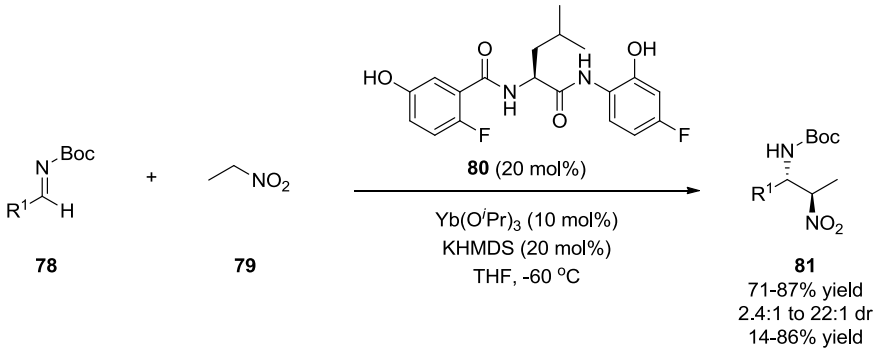


R^1 = Ph, 2-naphthyl, 2-furyl, 4-Me-C_6H_4, 3-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, $C_6H_5CH_2CH_2$;
R^2 = Me, Et.

Scheme 23– Enantioselective nitro-Mannich reaction between *N*-Boc-imines 74 and nitroacetates 75

[29] Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.

In 2010, Shibasaki and co-workers reported a catalytic asymmetric nitro-Mannich reaction with Yb/K heterobimetallic catalyst between *N*-Boc-imines **78** and nitroethane **79** (Scheme 24).[30] The β-nitroamines **81** were isolated in very good yields (77% in average) with low to excellent *anti* diastereoselectivity (2.4:1 to 22:1 dr) and low to very good enantiomeric excess (14% to 86%).

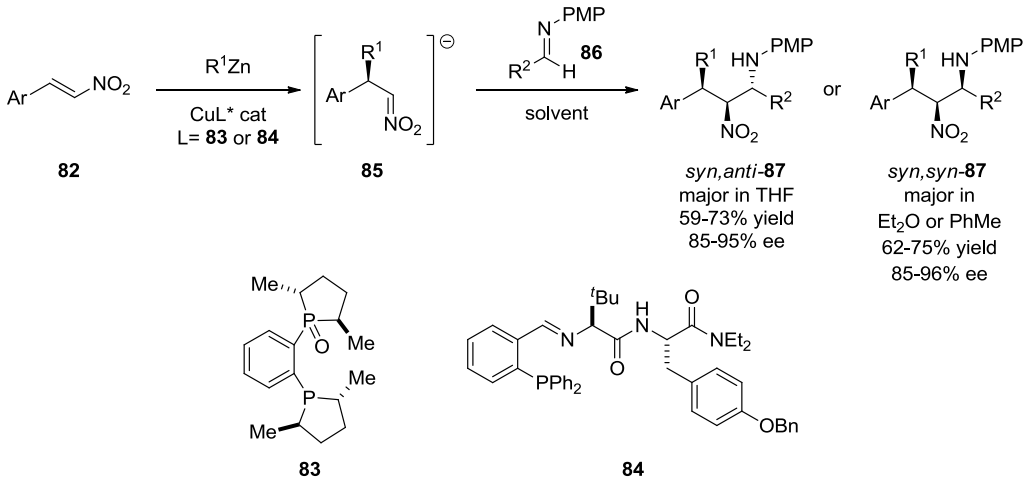


R^1 = Ph, 2-naphthyl, 4-Me-C_6H_4, 3-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F_3C-C_6H_4;

Scheme 24 – Enantioselective nitro-Mannich reaction with Yb/K heterobimetallic catalyst

More recently, Anderson *et al.* reported an enantioselective nitro-Mannich reaction between aromatic nitroalkenes **82** and a *N*-PMP-imine **86** to form β-nitroamines **87** with three contiguous stereocenters (Scheme 25).[31] First, a 1,4-addition of dialkylzinc to aromatic nitroalkenes **82**, catalysed by known copper-chiral ligand catalysts **83** and **84**, led to intermediates **85** which, upon treatment with *N*-PMP-imines **86** in the presence of TFA at -78 °C provided the desired products **87**. Very interestingly, the selective formation of the *syn*,*anti* or of the *syn*,*syn* diastereoisomers **87** was controlled by the choice of solvent. This work was particularly important as it represents one of the few examples of *syn*-selective nitro-Mannich reaction. The desired products **87** were obtained in moderate to good yields (59% to 75%) and very good to excellent enantiomeric excess (85% to 96%).

[30] Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Molecules* **2010**, *15*, 1280.
[31] Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961.



Ar = Ph, 2-furyl, 2-thienyl, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 2-F_3C-C_6H_4, 2-MeO-C_6H_4;.
R^1 = Me, Et; R^2 = Ph, 2-furyl, 2-thienyl, 4-Me-C_6H_4, 4-Cl-C_6H_4, *n*-Pn, CO_2Et

Scheme 25 – Solvent controlled formation of *anti*- and *syn*-β-nitroamines 87

In conclusion, various organometallic catalysts have been developed and used in the nitro-Mannich reaction to achieve high degrees of diastereo- and enantiocontrol. Other methodologies using organocatalysts have also been developed and they are the focus of the following section.

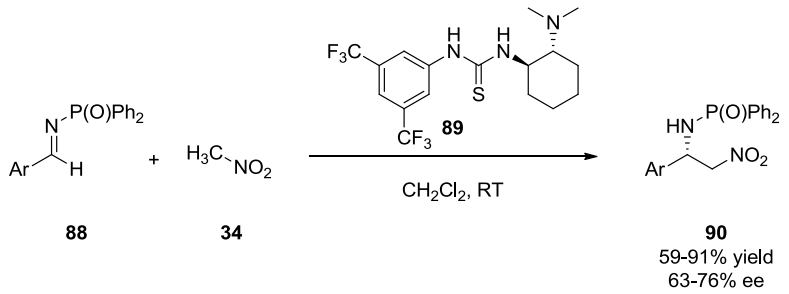
I.1.3 Stereoselective nitro-Mannich reaction using organocatalysts[32]

In the past years, we have witnessed a growing interest for organocatalysis as organocatalysts are generally cheaper, more stable and less toxic than organometallics compounds. In other words and more practically, they are nice and easy to use and to prepare and they do not require to be handled in a glove box. In this respect, the nitro-Mannich reaction was considered a perfect model system to test the efficiency of new organocatalysts.

The first enantioselective nitro-Mannich reactions using organocatalysts were reported independently by Takemoto and Johnston in 2004 using different organocatalysts. Takemoto and co-workers described the enantioselective reaction of nitromethane **34** with aromatic *N*-phosphinoylimines **88** catalysed by the thiourea derivative **89** (Scheme 26).[33] The scope of the

[32] For a review: Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401.
[33] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.

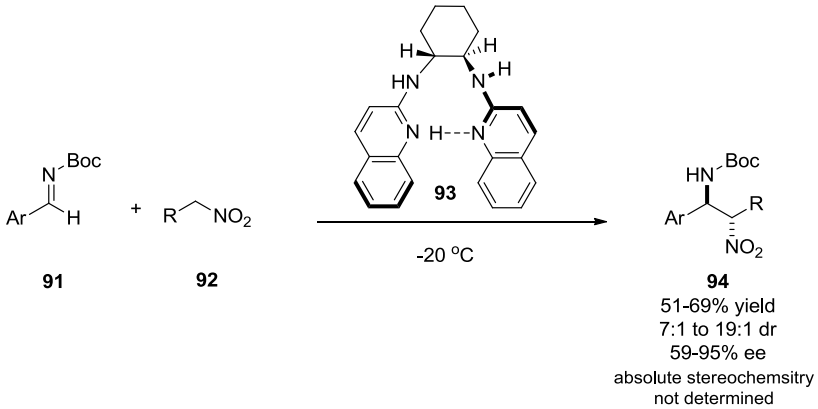
reaction was limited to aromatic and heteroaromatic *N*-phosphinoylimines **88** but the desired β-nitroamines **90** were isolated in moderate to very good yield (57% to 91%) and moderate to good enantioselectivities (63% to 76% ee).



Ar = Ph, 2-furyl, 2-thienyl, 2-pyridyl, 2-naphthyl, cinnamyl, 4-Me-C_6H_4, 4-Cl-C_6H_4.

Scheme 26 – First organocatalytic enantioselective nitro-Mannich reaction by Takemoto

The catalyst utilised by Johnston *et al.* allowed the enantioselective reaction of aromatic *N*-Boc-imines **91** and nitroalkane **92** catalysed by the bisamidine ligand **93** with a higher degree of enantiocontrol (Scheme 27).[34] The desired *anti*-β-nitroamines **94** were obtained in moderate to good yields (51% to 69%), very good to excellent *anti*-diastereoselectivity (7:1 to 19:1 dr) and moderate to excellent enantiomeric excess (59% to 95%). However the scope of the reaction was fairly limited and was restricted to aromatic groups bearing electron withdrawing substituents.



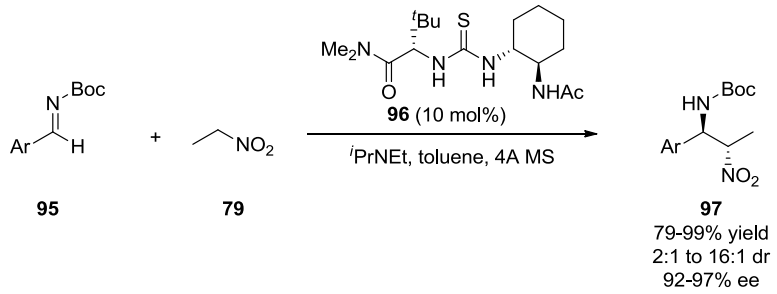
Ar = Ph, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-CF_3O-C_6H_4, 4-Cl-C_6H_4, R = H, Me.

Scheme 27 – First organocatalytic enantioselective nitro-Mannich reaction by Johnston

By using a different thiourea derivative **96** than the one used by Takemoto, Jacobsen's group was able to increase the yield and the enantioselectivity of the nitro-Mannich reaction between aromatic

[34] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

N-Boc-imines **95** and nitroethane **79** (Scheme 28).[35] The desired *anti*-β-nitroamines **97** were formed in excellent chemical yield (93% in average), moderate to excellent *anti*-diastereoselectivity (2:1 to 16:1 dr) and excellent enantiomeric excess (95% in average). In addition the reaction was successfully performed with 2-nitropropane **13**, and the newly formed product bearing a quaternary centre was isolated in excellent yield (87%) and enantiomeric excess (92%).

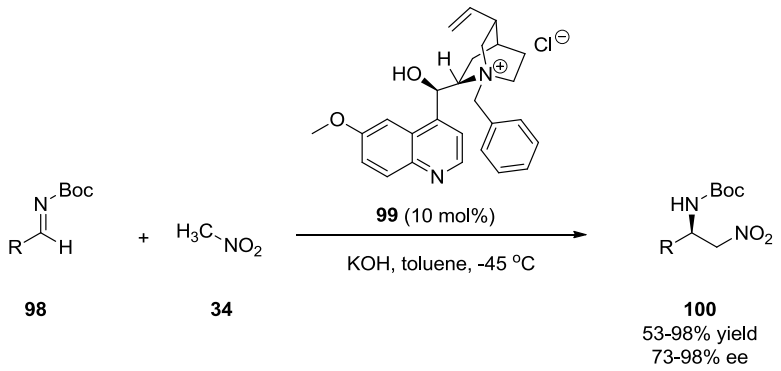


Ar = Ph, 2-furyl, 2-pyridyl, 2-naphthyl, 4-Me-C_6H_4, 3-Me-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 2-Cl-C_6H_4, 4-Meo-C_6H_4,

Scheme 28 – First organocatalytic enantioselective nitro-Mannich reaction by Takemoto

The first asymmetric nitro-Mannich reaction catalysed by a phase-transfer-catalyst (PTC) was reported by Ricci's group in 2005 and they described the reaction of nitromethane **34** with alkyl and aryl Boc-imines **98** (Scheme 29).[36] This work is particularly valuable as the scope of the reaction, usually limited to aromatic imines, included a wide variety of alkyl imines. The reaction with N-benzyl quininium chloride **99** provided the corresponding β-nitroamines **100** in excellent yield (85% in average) and very good to excellent enantioselectivity (73% to 98% ee).

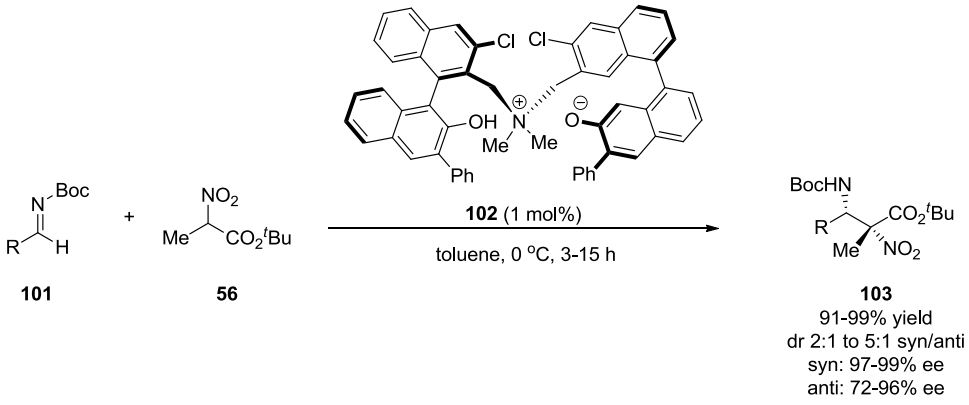
[35] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[36] Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975.



R = Ph, 2-furyl, 1-naphthyl, 4-MeO-C_6H_4, 2-Br-C_6H_4, $PhCH_2CH_2$, Cy, ^{i}Pr, Et, Me.

Scheme 29 – First enantioselective nitro-Mannich reaction catalysed by PTC

In 2008, Ooi's group designed an efficient bifunctional organocatalyst **102** that utilised the lowest catalyst loading reported so far (1 mol%) for the nitro-Mannich reaction of *N*-Boc-imines **101** with ^{t}butyl-2-nitropropionate **56** to form α-nitro-β-amino esters **103** bearing a quaternary centre (Scheme 30).[37] The diastereomeric ratio in this reaction was moderate (2:1 to 5:1), however the efficiency (95% yield in average) and the degree of enantioselectivity (98% and 90% ee in average for the *syn* and *anti* diastereomers respectively) were exceptionally high.



R = Ph, 2-furyl, 1-naphthyl, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-MeOCO-C_6H_4, 2-Me-C_6H_4, $PhCH_2CH_2$, $CH_3(CH_2)_7$

Scheme 30 – Enantioselective nitro-Mannich reaction catalysed by bifunctional catalyst 102

Since its early discovery in 1897, the nitro-Mannich reaction had received a shy interest from the synthetic community for the majority of the 20th century. However, since the late nineties various methods have been developed with the aim of improving on the efficiency, the stereoselectivity and

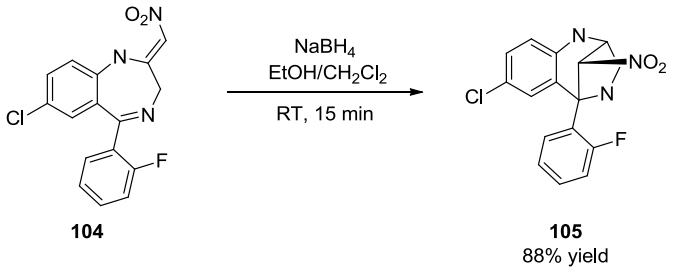
[37] Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878.

the generality of the nitro-Mannich reaction. Nowadays, there exist a wide variety of catalysts and methods that can be used on various substrates to perform nitro-Mannich reaction with high degrees of both diastereo- and enantiocontrol. Accordingly, the nitro-Mannich is just starting to be used in synthesis.

I.1.4 The nitro-Mannich reaction in synthesis

Very few syntheses of natural products or biologically active compounds report the use of a nitro-Mannich reaction. This is probably due to the fact that the development of efficient and stereoselective methodologies were only reported in the past decade and that the nitro group is not available in a lot of commercial compounds.

The first time a nitro-Mannich reaction was described in a synthesis it was the result of serendipity. Indeed, in 1978, Walser *et al.* reported,[38] in the work towards the synthesis of imidazobenzodiazepines, the unexpected cyclisation of **104** upon treatment with sodium borohydride. Instead, upon reduction of the nitro alkene to the corresponding nitro-alkane, a nitro-Mannich reaction took place and formed the bridged compound **105** (Scheme 31).

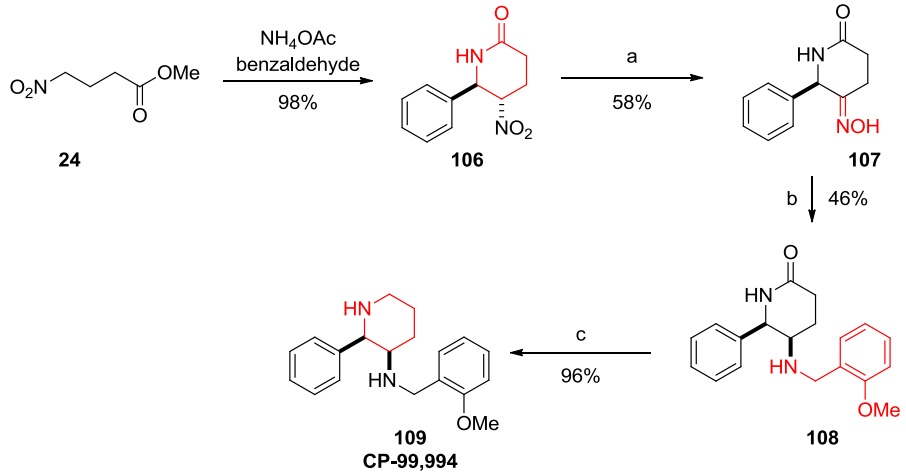


104 **105** 88% yield

Scheme 31 – First nitro-Mannich reaction reported in synthesis

In 1993, Desai and co-workers reported the first synthesis of a biologically active compound CP-99,994 **109** *via* a nitro-Mannich reaction as key step (Scheme 32). [39] The *trans* 5-nitropiperidin-2-one ring **106** was efficiently and selectively constructed in one step *via* a nitro-Mannich / lactamisation cascade in 98% yield. Three subsequent steps afforded the synthesis of CP-99,994 **109** in 26% overall yield.

[38] Walser, A.; Benjamin, L. E.; Flynn, T.; Mason, C.; Schwartz, R.; Fryer, R. I. *J. Org. Chem.* **1978**, *43*, 936.
[39] Desai, M. C.; Thadio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831.



a)i) ^{t}BuOK-O_3, -78 °C; Me_2S; ii) $NH_2OH.HCl$; b) i) Raney-Ni, H_2; ii) 2-MeO-benzaldehyde, $NaBH_3CN$, 4Å MS; iii) SiO_2 gel column; c) i) BMS, THF, reflux; ii)HCl, Et_2O.

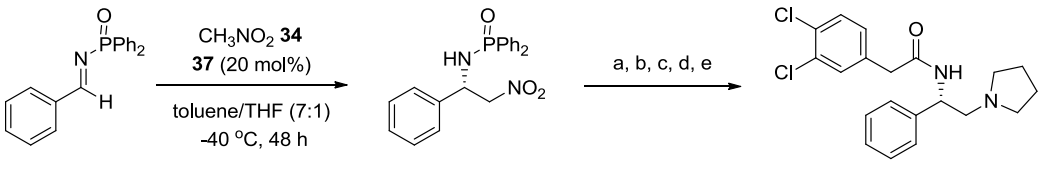
Scheme 32 – First deliberate nitro-Mannich reaction in synthesis

In 2002, Shibasaki and co-workers reported the first synthesis of biologically active compounds based on an asymmetric nitro-Mannich reaction key step. Indeed ICI-199441 **112** and CP-99,994 **109** were both synthesised in six steps from benzaldehyde imine **110** (Scheme 33) *via* an initial enantioselective nitro-Mannich reaction catalysed by heterobimetallic complexes of Yb **37** and ALB-KO-^{t}Bu respectively.[40]

After its formation *via* the nitro-Mannich reaction of imine **110** and nitromethane **34**, β-nitroamine **111** (obtained in >99% ee after recrystallisation) subsequently underwent a reduction with Raney-Ni and a reductive alkylation to construct the pyrrolidine ring of **112**. This was followed by the deprotection of the phosphinoyl group, a methylation and an acylation reaction to form ICI-199441 **112** in 35% yield overall.

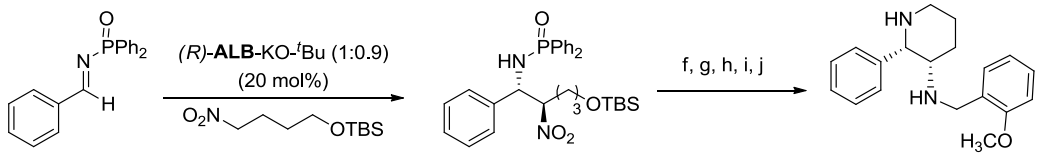
Similarly, removal of the TBS group of β-nitroamine **113** followed by a Dess-Martin oxidation, and spontaneous cyclisation allowed the formation of the piperidine of **109**; subsequently, the stereocenter was epimerized, the nitro group reduced with Zn, the *o*-anisyl group was introduced by reductive alkylation, and treatment by $LiAlH_4$ simultaneously afforded the deprotection of the phosphinoyl group and the reduction the enamine moiety. CP-99,994 **109** was isolated in 13% over six steps.

[40] Tsuritani, N.; Yamada, K-I.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276.



110 **111** 79% yield >99% ee **112** **ICI-199441** 57% yield

a) Raney-Ni, H_2, EtOH, RT, 92%; b) $OHC(CH_2)_2CHO$, $NaBH_3CN$, EtOH, pH 5, 0 °C, 81%; c) 1.5M HCl-EtOH, RT, 98%; d) i) HCO_2Ac, -20 °C, ii) $LiAlH_4$, reflux, 90% over 2 steps; e) $ArCH_2COCl$, CH_2Cl_2, RT, 87%, Ar=3.4-dochlorophenyl.

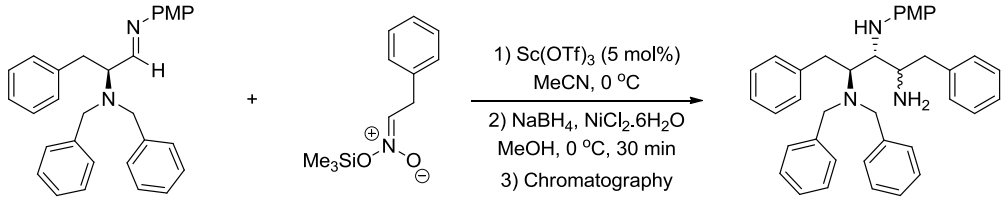


110 **113** 90% yield 6:1 dr, 77% ee **109** **CP-99,994** 15% yield

f) HF-pyridine, THF, 0 °C to RT, quant.; g) Dess-Martin periodinane, CH_2Cl_2, RT, 14h, 86%; h) i) TMSCl, DBU, CH_2Cl_2, 0 °C, 1h; ii) AcOH, -78 °C, 15 min, 83% over 2 steps; i) Zn, NH_4Cl, $MeOH/H_2O$, RT, 85%; j) *o*-anisaldehyde, $NaBH_3CN$, 3A MS, MeOH, RT, 3h, 81%; k) $LiAlH_4$, THF, RT, 30%.

Scheme 33 –Enantioselective synthesis of ICI-199441 and CP-99,994

The following year, Ricci's group described the synthesis of HIV protease inhibitors which included a nitro-Mannich reaction as a key step. Indeed, the reaction of enantiopure *N*-PMP-imine **114** and trimethylsilyl nitropropanoate **115** was catalysed by $Sc(OTf)_3$ to form **116** in 66% yield after subsequent reduction of the nitro group (Scheme 34). The diastereocontrol was poor (1.5:1 dr) but the separation of the *anti,syn*-major and *anti,anti*-minor diastereoisomers was afforded by column chromatography.



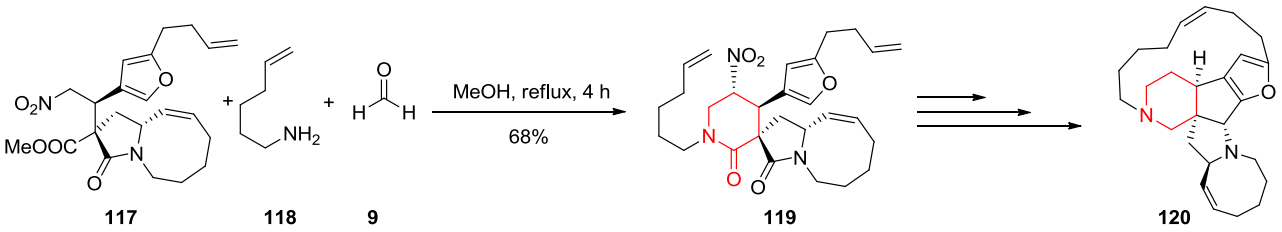
114 **115** **116** 66% yield, dr 1.5:1

Scheme 34 – Enantioselective synthesis of HIV protease inhibitors

In 2009, Dixon *et al.* published the total synthesis of nakadomarin A **120** featuring a nitro-Mannich / lactamisation cascade as one of the key steps (Scheme 35).[41] Indeed the six-membered ring of the spiro intermediate **119** was synthesised from the reaction of nitro-alkane **117** with formaldehyde **9**

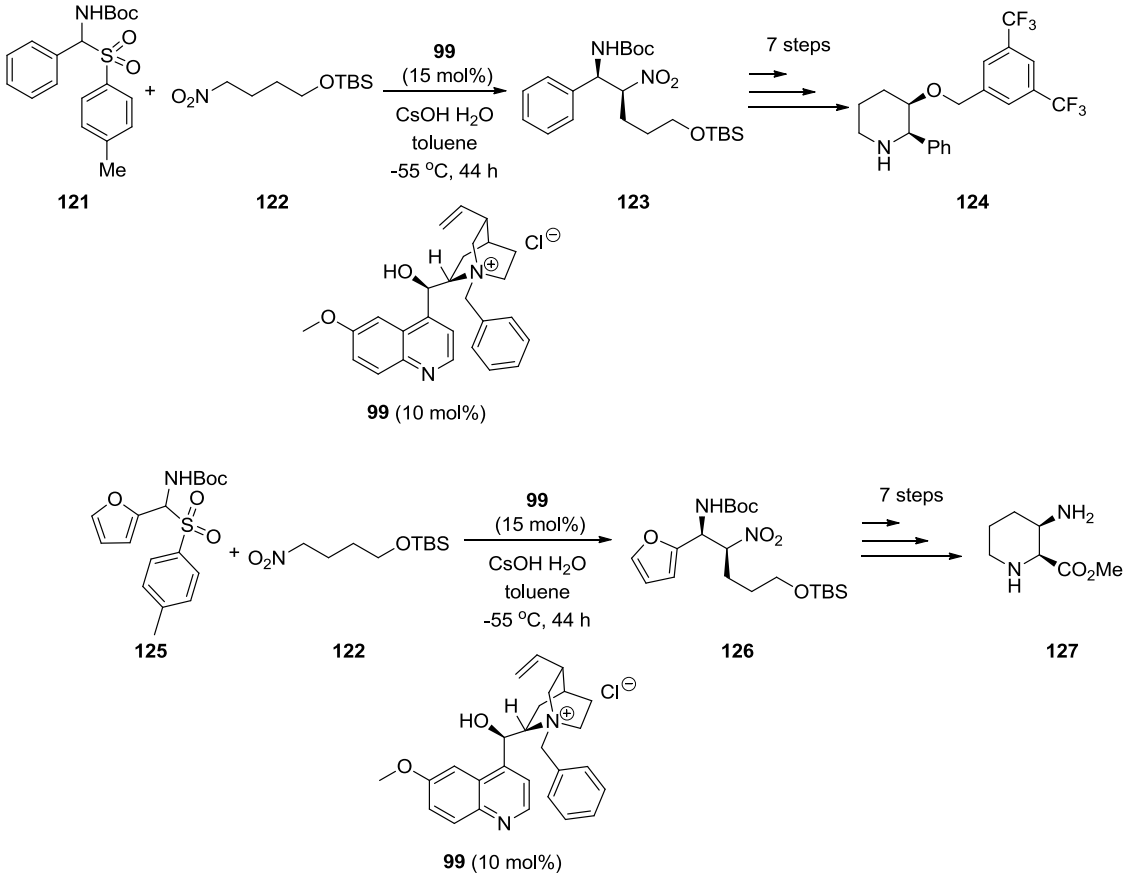
[41] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131,* 16632.

and 6-aminohex-1-ene **118** in refluxing methanol in 68% yield. The total synthesis of Nakadomarin A **120** was completed in 12 steps (longest linear sequence).



Scheme 35 – Nitro-Mannich / lactamisation cascade in the total synthesis of Nakadomarin A

More recently, Kumaraswany et al. reported the synthesis of L-(-)-733,061 **124** and (2S,3R)-methyl-3-aminopiperidine-2-carboxylate **127** *via* a catalytic enantioselective nitro-Mannich reaction which, in one step, established the desired stereocenters with high degrees of selectivity (Scheme 36).[42] The rest of the synthesis required an additional 7 steps in both cases.

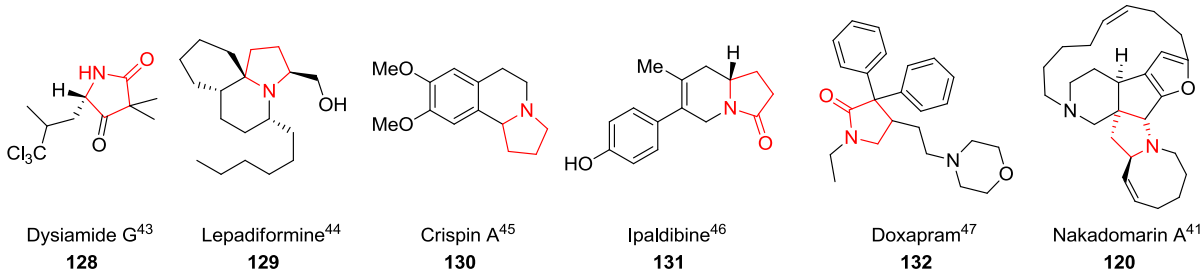


Scheme 36– Synthesis of L-(-)-733,061 and (2S,3R)-methyl-3-aminopiperidine-2-carboxylate

[42] Kumaraswany, G.; Pitchaiah, A. *Tetrahedron* **2011**, *67,* 2536.

I.2 The synthesis of pyrrolidin-2-ones

Pyrrolidine and pyrrolidinone rings are common motifs found in many biologically active natural products and drugs.[43, 44, 45, 46, 47, 41] The structures of these compounds range from relatively simple monocyclic pyrrolidinone, such as Dysiamide G **128**, to architecturally complex polycyclic ring system, such as the one found in the alkaloid nakadomarin A **120** (Figure **2**).



Dysiamide G[43] **128** | Lepadiformine[44] **129** | Crispin A[45] **130** | Ipaldibine[46] **131** | Doxapram[47] **132** | Nakadomarin A[41] **120**

Figure 2 – Pyrrolidine and pyrrolidin-2-one heterocycles in biologically active natural products and drugs

The abundance of the pyrrolidin-2-one motif in desirable targets has led to considerable interest from the synthetic community and various methodologies exist for their synthesis. However, to the best of our knowledge, there are no general method that can routinally be employed to access a wide variety of pyrrolidin-2-ones bearing different substituents around the ring. To illustrate this, we will present a selection of some of the most general examples of pyrrolidin-2-ones synthesis.

In 1947, Franck, Schmitz and Zeidman reported the synthesis of 1,5-dimethyl-2-pyrrolidinone **136** on a 200 g scale starting from levulinic acid **133** (Scheme 37).[48] Imine **134**, formed from the condensation of ketone **130** and methylamine, was subsequently reduced by Raney-nickel to afford amine **135**. Spontaneous lactamisation afforded 1,5-dimethyl-2-pyrrolidinone **136** in 75% yield after purification by distillation.

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[43] (a) Carmely, S.; Gebreyesus, T.; Kashman, Y.; Skelton, B. W.; white, A. H.; Yosief, T. *Aust. J. Chem.* **1990**, *43*, 1881. (b) Sauleau, P.; Retailleau, P.; Vacelet, J.; Bourguet-Kondracki, M.-L. *Tetrahedron* **2005**, *61*, 955.

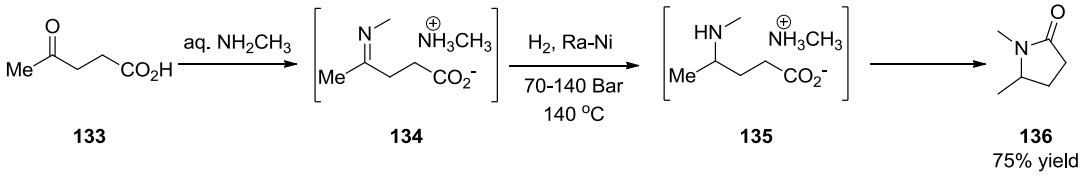
[44] Isolation: Rainey, D. P.; Smalley, E. B.; Crump, M. H.; Strong, F. M. *Nature* **1965**, *205*, 203.

[45] Isolation: Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Marine Drugs* **2005**, *3*, 78.

[46] Isolation : Courley, J. M.; Heacock, R. A; McInnes, A. G.; Nikolin, B.; Smith, D. G. *Chem. Commun*. **1969**, 709.

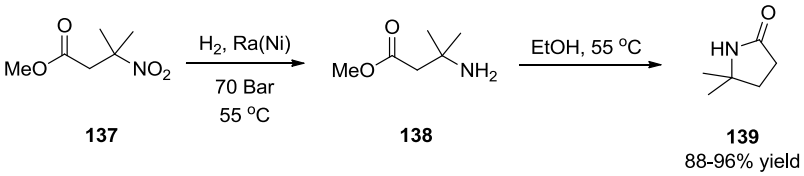
[47] (a) Robson, R. H.; Prescott, L. F. *Br J. Clin. Pharmacol.* **1979**, *7*, 81. (b) Anon *Federal Drug Re*gister **1975**, *40*, 17838. (c) Ward, J. W.; Gilbert, D. L.; Franko, B. V.; Woodard, G.; Mann, G. T. *Toxicology and applied Pharmacology* **1968**, *13*, 242.

[48] Frank, R. L.; Schmitz, W. R.; Zeidman, B. *Org. Syn. Coll. Col.* **1947**, *3,* 328.



Scheme 37 – Synthesis of 1,5-dimethyl-2-pyrrolidinone 136

In 1952, Moffett described the multi-gram synthesis of 5,5-dimethyl-2-pyrrolidinone **139** starting from methyl γ-methyl-γ-nitrovalerate **137**(Scheme 38).[49] Amine **138**, formed from the reduction with Raney-nickel of the nitro group of **137**, was cyclised in hot ethanol to afford 5,5-dimethyl-2-pyrrolidinone **139** in 88-96% yield after purification by distillation.

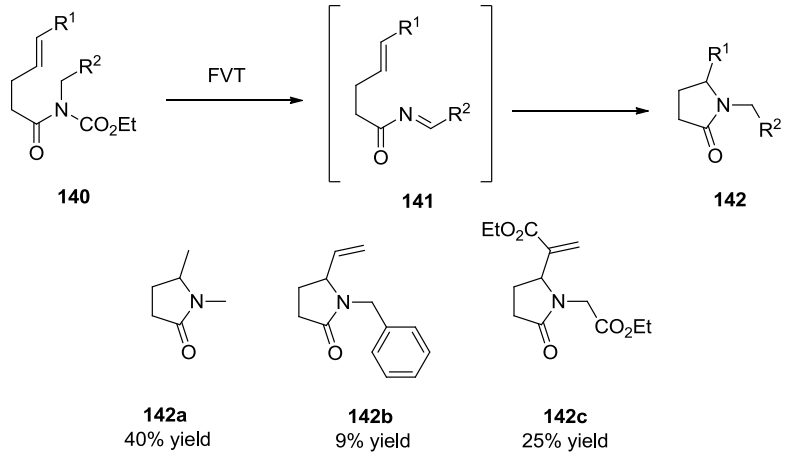


Scheme 38 – Synthesis of 5,5-dimethyl-2-pyrrolidinone 146

These early developments, allowed the efficient synthesis of pyrrolidi-2-ones but the scope of the reaction was limited.

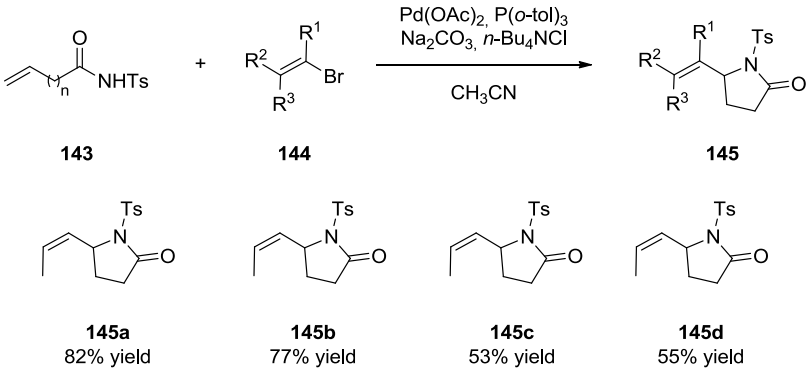
Fowler and co-workers reported the synthesis of 1,5-disubstitutedpyrrolidin-2-ones **142** *via* the flash vacuum thermolysis (FVT) of hydroxamic acid derivatives **140** to form *N*-acyl imines **141** which can subsequently undergo an intramolecular ene reaction (Scheme 39).[50] The approach is mechanistically interesting and original but the desired products **142** were formed in low to moderate yields (9% to 40%).

[49] Moffett, R.B. *Org. Syn. Coll. Col.* **1952**, *32,* 49.
[50] Lin, J-M.; Koch, K.; Fowler, F. W. *J. Org. Chem.* **1986**, *51*, 167.



Scheme 39 – Synthesis of 1,5-disubstitutedpyrrolidin-2-ones by FVT

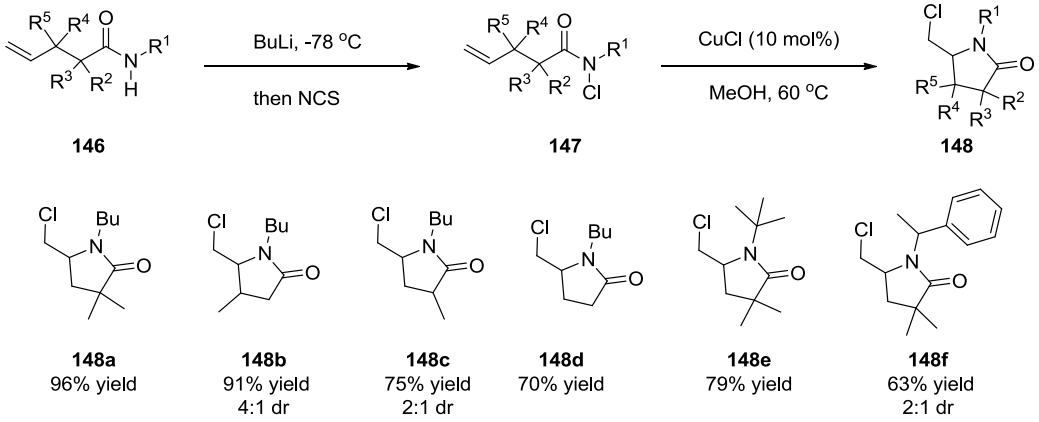
In 2003, Feringa and Minaard published an improved method with respect to the yield of the synthesis of pyrrolidin-2-ones *via* a tandem Heck / allylic substitution reaction (Scheme 40).[51] The reaction of ω olefinic *N*-tosylamines **143** and vinylic bromides **144** was catalysed by palladium to form the corresponding 1,5-disubstitutedpyrrolidin-2-ones **145** in moderate to very good yields (53% to 92%).



Scheme 40 – Synthesis of 1,5-disubstitutedpyrrolidin-2-ones *via* a tandem Heck / allylic substitution reaction

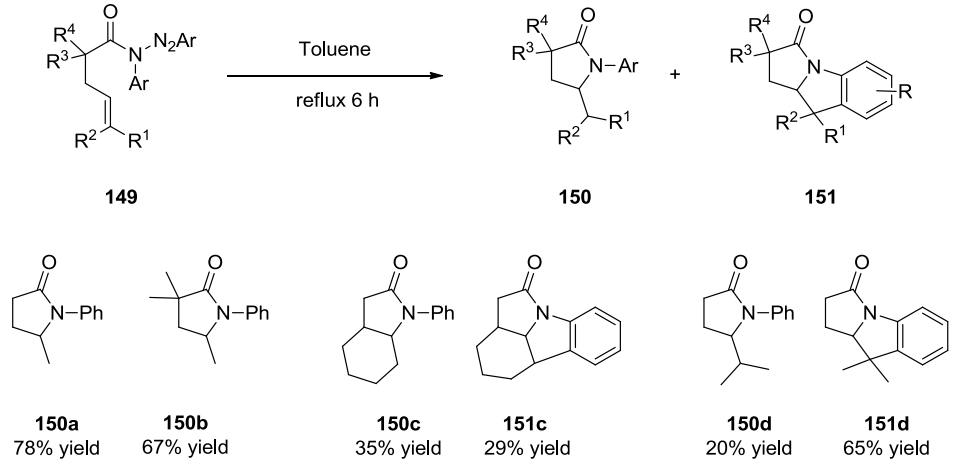
An improved methodology, in terms of scope and yield was reported by Gottlich's group in 2003.[52] They described the copper (I) chloride catalysed cyclisation of unsaturated N-chloroamides **147** to form the corresponding pyrroldin-2-ones **148** substituted in various positions (Scheme 41). The 1,3,5-trisubstituted pyrrolidinones **148** were obtained in good to excellent yield (63% to 96%).

[51] Pinho, P.; Minaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5,* 259.
[52] Schulte-Wülwer, I. A.; Helaja, J.; Gottlich, R. *Synthesis.* **2003**, *12,* 1886.



Scheme 41 – Synthesis of 1,3,5-trisubstitutedpyrrolidin-2-ones

In 2005, Li *et al.* reported an intramolecular cyclisation reaction of amidyl radicals generated from *N*-acytriazenes to access pyrrolidin-2-ones **150** (Scheme 42).[53] They also found that the terminal substitution at the C=C double bond resulted in the formation of the fused polycyclic pyrrolidin-2-ones **151** and that the degree of substitution had a strong influence on the chemoselectivity of the reaction.

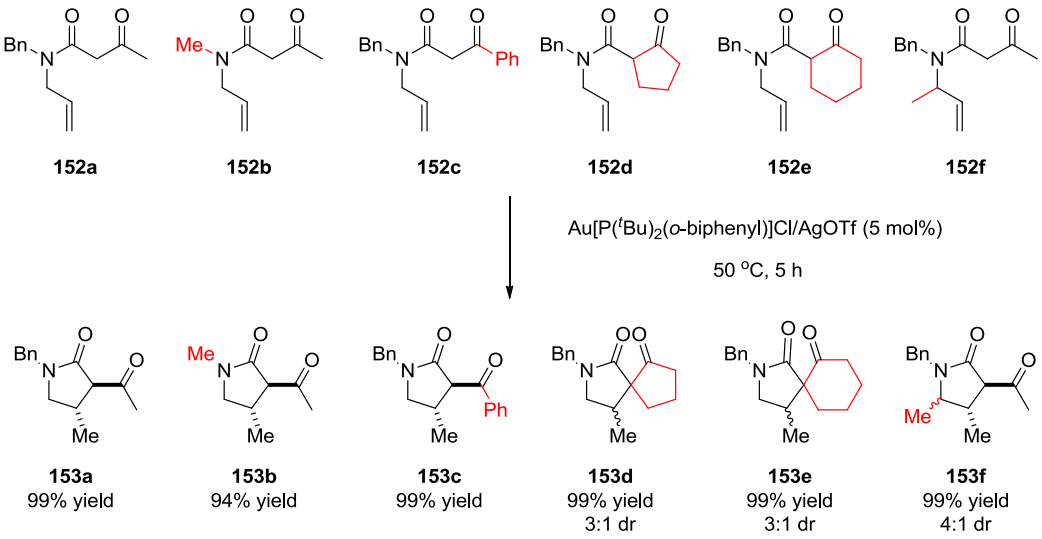


Scheme 42 – Synthesis of pyrrolidin-2-ones 150 and fused polycyclic pyrrolidin-2-ones 158

More recently, Che *et al.* developped a highly efficient gold catalysed intramolecular addition of β-ketoamides to unactivated alkenes moieties of **152** for the synthesis of pyrrolidin-2-ones **153** (Scheme 43).[54] The scope of the reaction was broad and allowed various substitution patterns at the 1, 3, 4 and 5 positions (**153a**, **153b**, **153c** and **153f**) and even enabled the synthesis of spiro products

[53] Lu, H.; Li, C. *Tetrahedron Letters.* **2005**,46, 5983.
[54] Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129,* 5828.

(**153d** and **153e**). The reaction was extremely efficient: pyrrolidinones **153** were isolated in excellent yield (98% in average) with only 5% catalyst loading.



Scheme 43 – Synthesis of pyrrolidin-2-ones 153

In this DPhil work, we proposed to develop new one-pot cascade reaction involving a nitro-Mannich reaction in order to easily access highly substituted heterocycles containing a nitrogen atom; and we will mainly focuse on pyrrolidin-2-ones.

CHAPTER 1

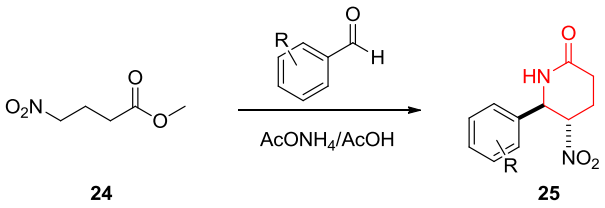
Synthesis of 1,5-Disubstituted-4-nitropyrrolidinones

via

a Nitro-Mannich / Lactamisation Cascade

1.1 Context

A reaction cascade, involving an initial nitro-Mannich reaction between a nitroalkane and an imine (cyclic or acyclic formed *in situ* or otherwise), followed by an irreversible lactamisation, was first reported in the literature in the 1970's, independently by Muhlstadt[55] *et al.* and Jain[56] *et al*. Both research groups described the reaction between methyl 4-nitrobutanoate **24**, an aromatic aldehyde and ammonium acetate to form the corresponding *trans* piperidinone **25** (Scheme 44).



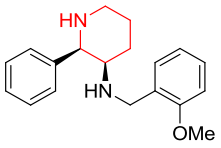
24 **25**

R= Me, OMe, Cl, $N(Me)_2$, CN, NO_2, Br

Scheme 44 - First syntheses of piperidinone *via* a nitro-Mannich / lactamisation cascade

In both publications, the scope of the reaction was narrow and included only a small number of substituted aromatic aldehydes.

Twenty years later, Desai *et al.* studied this reaction further, as they found it suitable for exploring the structure activity relationship (SAR) of a highly potent substance P antagonist CP-99,994 **109**.[57]

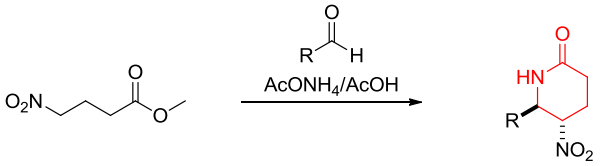


109

Figure 3 - CP-99,994

A library of *trans* piperidinones **154** was synthesized from methyl 4-nitrobutanoate **24**(Scheme 45) in good to excellent yields (67% to 98%), and it appeared that the reaction was facile, general and tolerated a wide variety of aldehydes, such as aromatic, heteroaromatic, alicyclic, and conjugated examples.

[55] Mühlstädt, M.; Schulze, B. *J. F. Prakt. Chem.* **1975**, 919.
[56] Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, *615*.
[57] Desai, M. C.; Thadio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831.

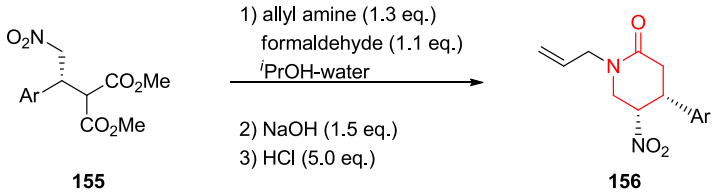


24 **154**

R= Ph, cyclohexyl, ^{t}butyl, 2-furyl, 2-thiophenyl, 3-pyridyl.

Scheme 45 - Synthesis of piperidinones 4

In 2007, Xu and co-workers published a similar reaction cascade starting from enantiomerically pure nitroalkanes **155**. A small range of nitroalkanes **155** bearing different aromatic groups, obtained in one step from an enantioselective Michael addition of malonates to nitrostyrenes, were treated with formaldehyde and allylamine in *iso*-propanol at 55 °C (Scheme 46). The corresponding piperidinone **156** were formed in moderate to good yields (62% to 81% yield).[58]



155 **156**

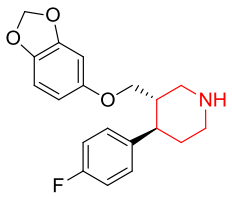
Ar = 4-F-C_6H_4, Ph, 4-Cl-C_6H_4, 4-Me-C_6H_4, 3-pyridine, 4-MeO-C_6H_4

Scheme 46 - Synthesis of *N*-substituted piperidinone 156 *via* a nitro-Mannich / lactamisation cascade

Upon decarboxylation, the major diastereoisomer isolated was the *cis* isomer. The Xu group also found that under acidic epimerisation conditions, the *cis* diastereoisomer could be formed with excellent diastereocontrol (dr 32:1) and, upon exposure to weak bases, the thermodynamically favored *trans* isomer could be isolated with a moderate diastereomeric ratio of 1:5. Finally, the selective preparation of the *trans* diastereoisomer was performed *via* a dynamic crystallization-driven process in 76% yield and 98% purity (by HPLC).

In the Dixon group, a first nitro-Mannich / lactamisation cascade was employed in the enantioselective formal synthesis of (3S, 4R)-paroxetine **157** (Figure **4**).[59]

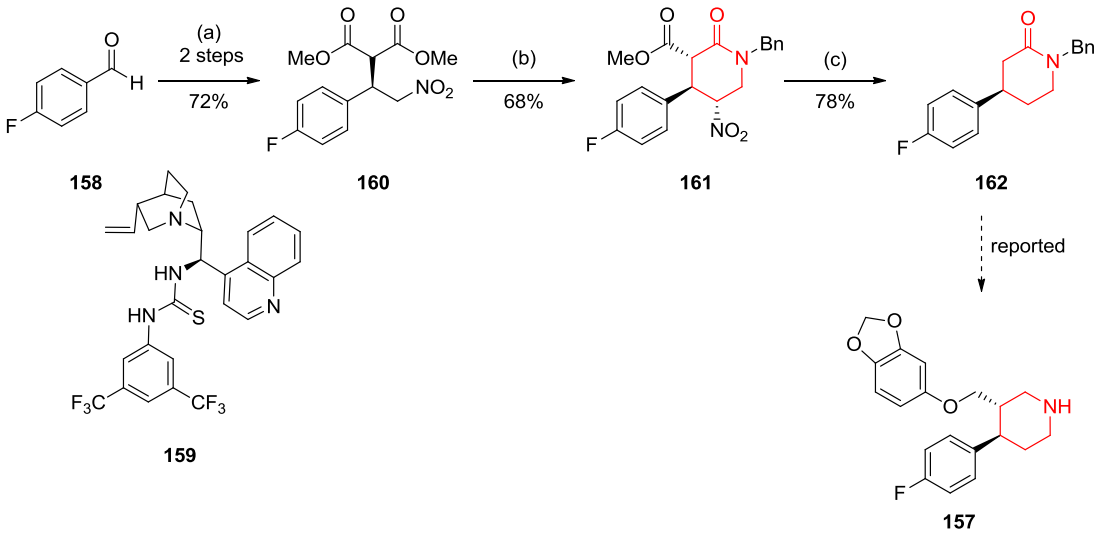
[58] Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669.
[59] Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10,* 1389.



157

Figure 4 - (3S, 4R)-paroxetine 7

The enantioenriched Michael adduct **160** was reacted with benzylamine and formaldehyde **9**, in boiling methanol for 16 hours to lead to the δ-lactam **161**, as a single diastereoisomer, in 68% yield (Scheme 47). The reductive removal of the nitro group, using a modification of the Ono protocol,[60] also facilitated the decarboxylation. The synthesis of piperidinone **162** was permitted in one pot and it constituted a formal synthesis of (3S, 4R)-paroxetine **157**.



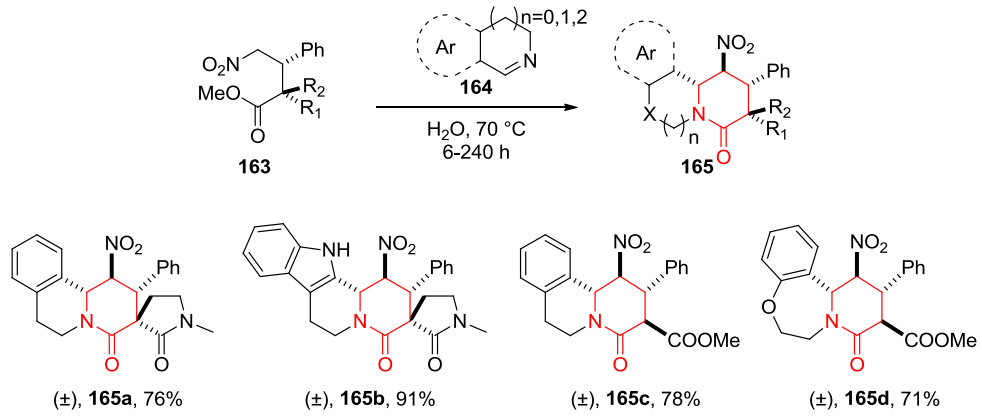
(a) i) $MeNO_2$, NH_4OAc, THF, reflux, 24h; ii) Dimethylmalonate, thiourea organocatalyst **159**, CH_2Cl_2, -20 °C, 72h;(b) CH_2O **9**, $BnNH_2$, MeOH, reflux, 16h. (c) $^nBu_3SnH$, AIBN, toluene, reflux, 16h.

Scheme 47 - A formal synthesis of (3S, 4R)-paroxetine 157 *via* a nitro-Mannich / lactamisation cascade

Since the previous publications described a fairly limited reaction scope, the nitro-Mannich / lactamisation reaction was investigated further in the Dixon group. This lead to the development of a new methodology for the synthesis of fused polycyclic piperidinones **165** *via* a nitro-Mannich / lactamisation cascade between complex nitroalkane precursors **163** and various cyclic imines **164**. After several optimisation studies, this reaction was found to proceed best in water heated to 70 °C.

[60] Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1750.

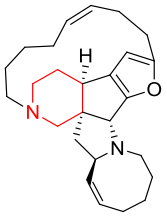
A range of five, six and seven-membered ring imines **164** were used along with various nitroalkanes **163**, and selected examples are shown in Scheme 48.[61]



Scheme 48 - A direct diastereoselective synthesis of fused polycyclic piperidinone derivatives 165

The reaction was found to be broad in scope, and 12 new fused polycyclic compounds **165** were synthesized in a very good average yield (72%) and excellent diastereocontrol (dr > 98:2).

Furthermore the utility of this methodology was demonstrated in the total synthesis of nakadomarin A **120** (Figure 5) published by Dixon *et al.* in 2009.[62]

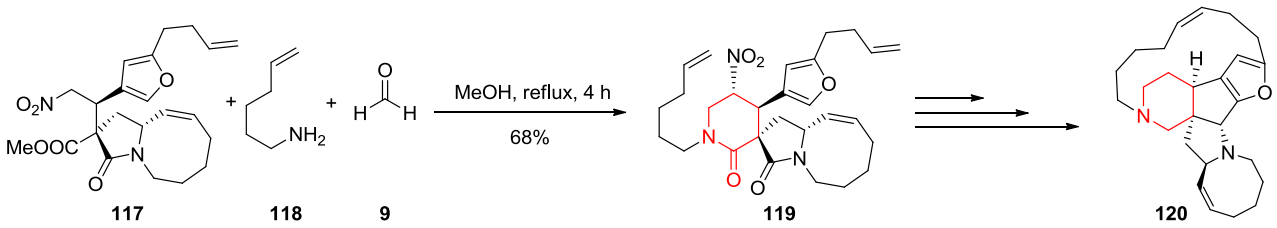


120

Figure 5 - Nakadomarin A

In this total synthesis, a nitro-Mannich / lactamisation cascade was used to synthesize the six-membered ring of nakadomarin A **120**. Nitro-alkane **117** was reacted with formaldehyde **9** and 6-aminohex-1-ene **118** in refluxing methanol for 4 hours to obtain the corresponding piperidinone **119** in 68% yield (Scheme 49).

[61] Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10,* 4267.
[62] Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131,* 16632.



Scheme 49 - A nitro-Mannich / lactamisation cascade in the total synthesis of Nakadomarin A

These previous studies highlighted the utility of a nitro-Mannich / lactamisation cascade as a synthetic tool: the reaction is broad in scope, very efficient (in one-pot and one-step, various reactions occurred and several chemical bonds are formed) and easy to perform. Nevertheless, in former work, such a cascade had never been used to synthesize the five-membered ring analogs, the nitro-pyrrolidin-2-ones. Thus, in a continuation of our studies we decided to investigate the synthesis of pyrrolidin-2-ones *via* a three component nitro-Mannich / lactamisation cascade.

1.2 Goal and preliminary studies

1.2.1 Pyrrolidine and pyrrolidinone heterocycles

Pyrrolidine and pyrrolidinone rings are common motifs found in many biologically active natural products and drugs[63, 64]. The structures of these compounds range from relatively simple monocyclic pyrrolidinone, such as dysiamide G **128**, to architecturally complex polycyclic ring system, such as the one found in the alkaloid nakadomarin A **120** (Figure 6).

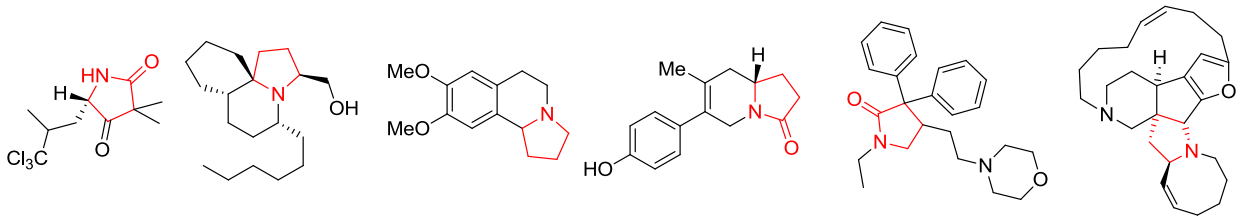


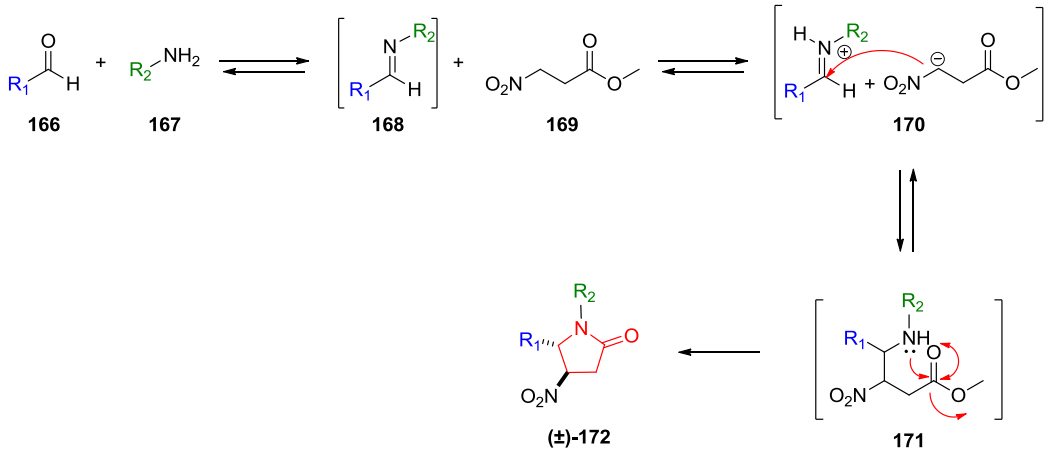
Figure 6 - Pyrrolidinone and pyrrolidinone rings in natural product and biologically active compounds

[63] (a) Carmely, S.; Gebreyesus, T.; Kashman, Y.; Skelton, B. W.; White, A. H.; Yosief, T. *Aust. J. Chem.* **1990**, *43*, 1881. (b) Sauleau, P.; Retailleau, P.; Vacelet, J.; Bourguet-Kondracki, M.-L. *Tetrahedron* **2005**, *61*, 955.
[64] Isolation: Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Marine Drugs* **2005**, *3*, 78.

The abundance of these motifs in desirable targets has led to considerable interest from the synthetic community. Despite the many publications in the field, assessment of the synthetic methods against a range of typical targets (from simple monocyclic to complex polycyclic) reveals that there is no one general method or strategy that can be routinely employed for the whole class of compounds. Accordingly we believed that the development of a new route would be useful in both pharmaceutical and natural products synthesis.

1.2.2 Our approach

Our proposed cascade is shown in Scheme 50. Treatment of an aldehyde **166** an with amine **167** should lead to the rapid formation of the imine intermediate **168** which is poised to undergo proton exchange with the acidic nitroalkane **169**. This mutually reactive ion pair **170** should then undergo carbon-carbon bond formation to give the nitro-Mannich product **171** which, through favourable positioning of the amine and the ester functionality, is able to undergo irreversible lactamisation to afford **172**.



Scheme 50 – Proposed nitro-Mannich / lactamisation cascade for the synthesis of pyrrolidin-2-ones 172

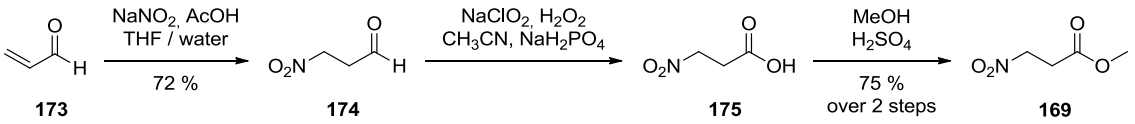
1.2.3 Synthesis of the starting material: methyl 3-nitropropanoate 169

Methyl 3-nitropropanoate **169** was prepared in 3 steps *via* a modification of literature procedures, starting from acrolein **173** (Scheme 51).[65] First, a nucleophilic addition of nitrite anion on acrolein **173**

[65] (a) Griesser, H.; Ohrlein, R.; Schwab, W.; Ehrler, R.; Jager, V. *Org. Synth.* **2004**, Coll. Vol. 10, 577. (b) Silva, P. C.; Costa, J. S.; Pereira, V. L. P. *Synth. Commun.* **2001**, *31*, 595.

provided 3-nitropropanal **174** in 72% yield. Then, a Pinnick oxidation on aldehyde **174** afforded 3-nitropropanoic acid **175** as a white solid after trituration in chloroform. Finally, methyl-3-nitropropanoate **169** was formed by esterification, catalyzed by concentrated sulfuric acid in boiling methanol in 75% yield over the two steps.

In order to form methyl-3-nitropropanoate **169** in one step, the addition of sodium nitrite was attempted directly on methyl acrylate. Unfortunately, only traces of product were formed. Methyl acrylate is probably not electrophilic enough to undergo such transformation.



Scheme 51 – A three steps synthesis of methyl 3-nitropropanoate 169

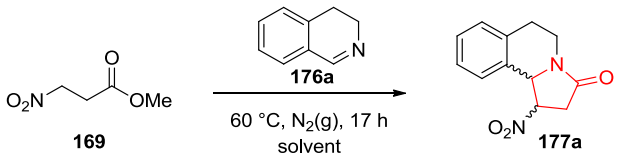
The sequence described above was therefore gradually scaled up from 500 mg scale, until it was performed on 40 g scale of acrolein to form the desired nitroester in 54% overall yield.

With methyl 3-nitropropanoate **169** starting material in hand, we were ready to start probing its reactivity towards a nitro-Mannich / lactamisation cascade.

1.2.4 Proof of principle

In order to probe the reactivity of methyl 3-nitropropanoate **169** in the nitro-Mannich / lactamisation cascade for the synthesis of pyrrolidinone heterocycles, it was decided to use a preformed cyclic imine **176** in to order limit the number of variables in the reaction and thus prevent side reactions as much as possible. Accordingly, a solvent screen was undertaken, for the reaction between methyl 3-nitropropanoate **169** and 3,4-dihydroisoquinoline **176a**, in order to isolate some of the desired fused polycyclic pyrrolidinone **177a** (Table 1).

The solvent screen was performed in sealed microwave vials (to maintain a constant volume of solvent), at 60 °C (lower than the boiling point of the solvent tested) and under an atmosphere of nitrogen (to maintain a constant pressure). The NMR yield was measured by ^{1}H NMR spectroscopy, against tribromobenzene as an internal standard, after an arbitrary period of 17 hours.

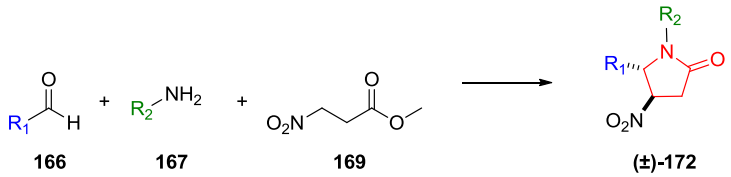


Entry	Solvent	177a (%)	dr
1	Water	-	-
2	MeOH	18%	2.5:1.0
3	CH_3CN	15%	1.5:1.0
4	THF	32%	3.0:1.0
5	$CHCl_3$	17%	3.2:1.0
6	Toluene	42%	4.2:1.0
7	Hexane	90%	1.4:1.0
8	Neat	100%	1.0:1.0

Table 1 – Solvent screen with preformed cyclic imines 176a

Previous studies on nitro-Mannich lactamisation cascades in our group[61,62] showed that polar protic solvents were preferred for the synthesis of piperidinone derivatives. However, in the present case of 5-membered ring formation, little or no conversion was observed in water and methanol (entries 1-2). Pleasingly, some product was observed with aprotic solvents (entries 3-6), and hexane and neat conditions provided the highest conversion. In toluene, the conversion remained moderate (42%), but the diastereocontrol (4.2:1.0) was the highest obtained.

These results were really encouraging and constituted a sound proof of principle. Nevertheless, our goal was to develop a three component cascade, where methyl 3-nitropropanoate **169** would be in the same pot along with an aldehyde **166** and an amine **167** (Scheme 52). Therefore we had to select another model system for all further studies.



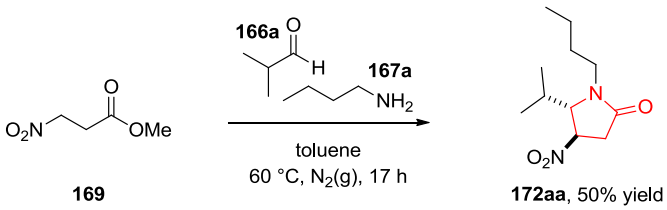
Scheme 52 – Goal: one pot / three component reaction

1.2.5 Model system

In order to develop a general method for the one-pot synthesis of pyrrolidinone **172**, starting from methyl 3-nitropropanoate **169**, it was important to choose wisely the aldehyde **166** and the amine **167** which were to constitute the model system. First, isobutyraldehyde **166a** was selected for three

reasons: it possesses a good reactivity, it is branched, which minimized the chance of getting side reactions such as the aldol reaction, and it is fairly stable. Second, butylamine **167a** was determined to be a good choice of linear primary amine: it is commercially available and free from steric hindrance, thus ensuring good reactivity.

A test reaction was then performed using methyl 3-nitropropanoate **169** (1.0 eq), isobutyraldehyde **166a** (1.0 eq), butylamine **167a** (1.0 eq) and toluene (0.1 mol/L) at 60 °C under an atmosphere of nitrogen (Scheme 53). The reaction was stopped after an arbitrary period of 17 hours and pleasingly, the desired pyrrolidinone (±)-**172aa** was isolated in 50% yield as a single diastereoisomer.



Scheme 53 - Model system

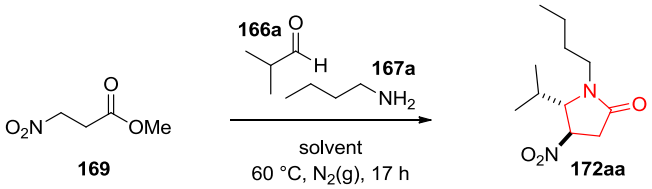
With a model system and a proof of principle in hand, we started the optimisation studies.

1.3 Optimisation studies

1.3.1 Solvent screen

1.3.1.1 Model system

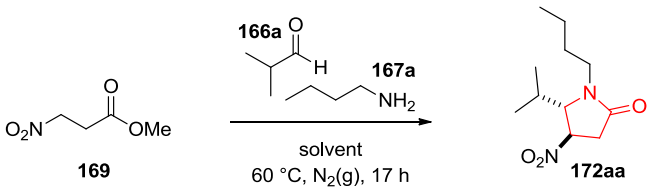
The results obtained from the first solvent screen with cyclic imines **176** (Table 1), suggested that apolar aprotic solvent, such as hexane and toluene, were preferred for this reaction. Nevertheless, the choice of solvent was not easy: the conditions providing the higher conversions (hexane, neat conditions) were different from the conditions leading to the higher degree of diastereocontrol (toluene). Therefore, it was decided to carry out a new solvent screen for the model system (Table 2). Similarly, the reactions were performed in sealed microwave vials, at 60 °C and under an atmosphere of nitrogen. The NMR yield was measured by ^{1}H NMR spectroscopy, against tribromobenzene as an internal standard, after an arbitrary period of 17 hours.



Entry	Solvent	Product 172aa (%)	Start. Mat. (%)	dr
1	Water	-	-	-
2	MeOH	17%	18%	> 98:2
3	CH_3CN	40%	60%	> 98:2
4	THF	43%	57%	> 98:2
5	$CHCl_3$	67%	33%	> 98:2
6	Toluene	50%	50%	> 98:2
7	Hexane	72%	17%	> 98:2
8	Neat	0%	-	-

Table 2 – Solvent screen for the model system

The results are very similar to the one obtained with cyclic imine **176a**, except that in all cases only one diastereoisomer was detected. The highest conversions were again provided by apolar aprotic solvents: chloroform, toluene and hexane. Surprisingly, the reaction performed under neat conditions did not show any traces of product or starting material, whereas in the case of cyclic imines (Table 1, entry 8), this set of conditions delivered a 100% conversion to the desired product **177a**. In order to investigate this matter further, three experiments were undertaken and the results are presented in Table 3.



Entry	Temp. (°C)	Time (h)	Conversion (%)
1	60 °C	17h	-
2	60 °C	1h	70%
3	RT	12h	100%

Table 3 – Investigation of the reactivity under neat conditions

The results presented in Table 3 confirmed that neat conditions reactions are very suitable for this reaction, as after stirring overnight at room temperature, the desired product **172aa** was formed quantitatively as a single diastereoisomer (entry 3). At 60 °C, 70% conversion was measured by ^{1}H NMR spectroscopy after only 1 hour and no sign of product or starting material could be found after

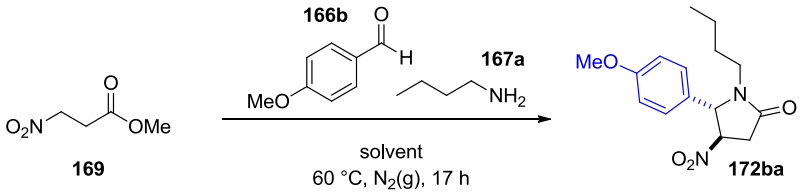
12 hours. This suggested that the pyrrolidinone **172aa** is probably sensitive to the reaction conditions and can degrade by prolonged exposure.

These results were very promising, but neat conditions can make it difficult to follow the reaction overtime, as it is difficult to sample a homogeneous fraction of the reaction mixture. Also, it was important at this point to probe the reactivity of other aldehydes **166** and amines **167** to ensure the generality of the method before optimising further.

1.3.1.2 Other systems

Two other reagents systems were selected to investigate the influence of the solvent on the reactivity and to allow a preliminary probe of the scope.

In the first system, butylamine **167a** remained and isobutyraldehyde **166a** was exchanged for *p*-methoxybenzaldehyde **166b**. The reaction was run under the same conditions as previous solvent screens, and with the three best solvents: toluene, chloroform and hexane. The results are displayed in Table 4.

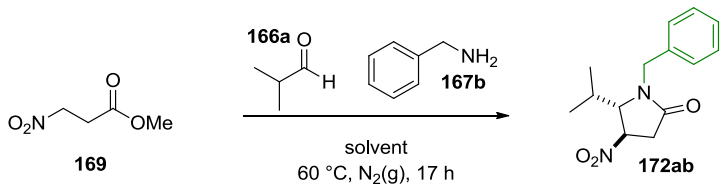


Entry	Solvent	Product 172ba (%)	dr
1	$CHCl_3$	38%	> 98:2
2	Toluene	58%	> 98:2
3	Hexane	28%	> 98:2

Table 4 – **Solvent screen for the reaction of butylamine 167a and *p*-anisaldehyde 166b**

Pleasingly, the desired product **172ba** was isolated in all three reactions, as a single diastereoisomer. The reaction performed in toluene provided the highest conversion after 17 hours at 60 °C.

In the second system, isobutyraldehyde **166a** remained and butylamine **167a** was exchanged for benzylamine **167b** (Table 5).



Entry	Solvent	Product 172ab (%)	dr
1	$CHCl_3$	50%	> 98:2
2	Toluene	15%	> 98:2
3	Hexane	82%	> 98:2

Table 5 – **Solvent screen for the system benzylamine/isobutyraldehyde**

Again, the desired product **172ab** was isolated in all three reactions as a single diastereoisomer but the conversion varied significantly with the solvent as shown in Table 5. Hexane gave an excellent conversion of 82% whereas in toluene, a poor conversion of 15% was measured by ^{1}H NMR spectroscopy.

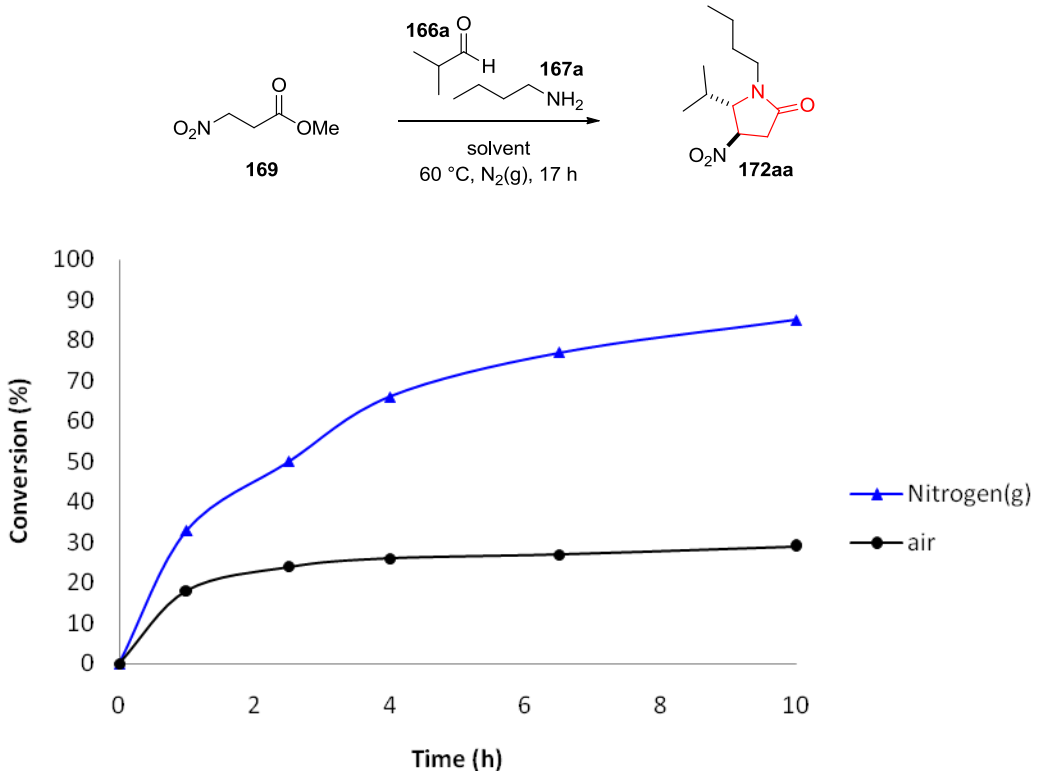
1.3.1.3 Choice of solvent

The results obtained from the four different solvent screens showed that apolar aprotic solvent, such as hexane, chloroform and toluene, are preferred for the reaction studied. The results did not allow us to easily select one solvent as the best one, since the solvent which provided the highest conversion, depended strongly upon the reagent system. Therefore we needed to consider other factors. Hexane was eliminated for the same reason neat conditions were: hexane does not solubilise the reaction mixture and therefore taking aliquots which are representative of the reaction at a given time is difficult. Both toluene and chloroform provided a homogeneous reaction mixture, but toluene was preferred because in the first solvent screen it was the solvent that provided the highest diastereocontrol. Also, toluene with its high boiling point (110 °C) allowed room for thermal optimisation. Accordingly, toluene was chosen for the rest of optimisation studies.

1.3.2 Oxygen in the reaction

Once the choice of the solvent was made, we ran the reaction several times to assess its reproducibility. Unfortunately, under what seemed to be similar reaction conditions (temperature, stoichiometry, concentration), the conversion obtained after 4 hours ranged from 28% to 72%. It appeared that the only remaining variable was the gaseous environment. Accordingly, we set up two

reactions: one open to the air, and another one which was vigourously degassed (by pumped/filled method), before being left under an atmosphere of nitrogen. Both reactions were monitored by ^{1}H NMR spectroscopy and the results are depicted in Graph 1.



Graph 1 - Influence of degassing the reaction mixture on the progress of the reaction

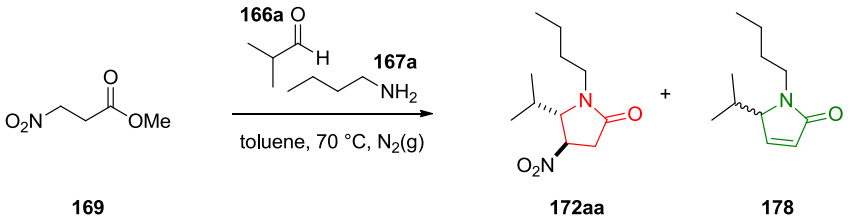
As seen in graph 1, the reaction which was not degassed stalled at about 30% conversion, whereas the reaction which was previously degassed proceeded smoothly up to 80% conversion as a single diastereoisomer. Therefore, it was evident that one of the components of the air was affecting the reaction. Further studies were undertaken to rationalise this result and will be discussed in chapter 5.

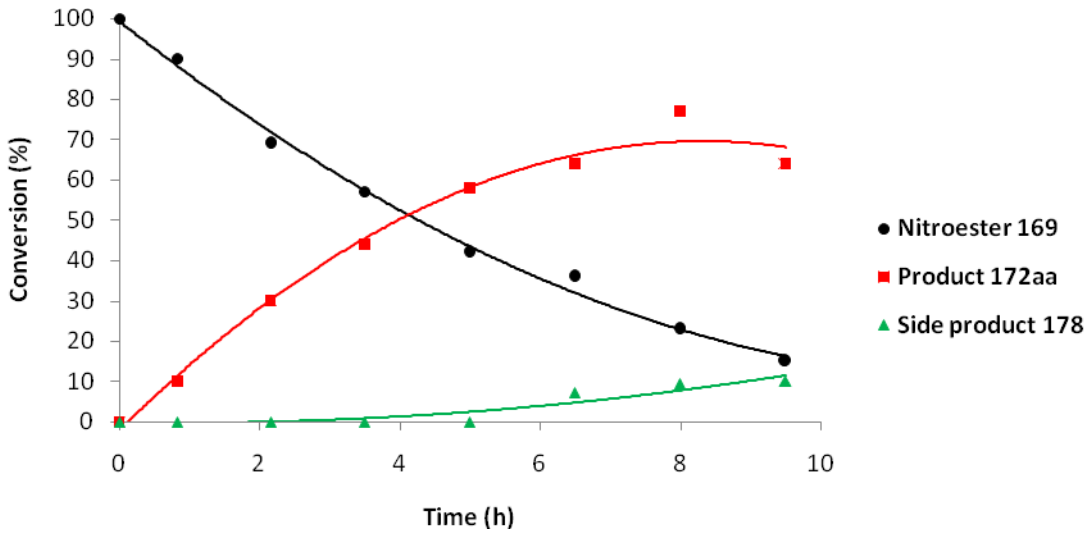
1.3.3 Further NMR studies to improve the overall yield of the reaction

After realising that the reaction mixture had to be pumped/filled with nitrogen, the reaction was found to be reproducible. Nevertheless, the isolated yield still needed improvement.

1.3.3.1 Isolation of a side product

Further NMR studies were undertaken to improve the yield of the reaction. The model reaction was set up and the conversion was monitored closely by ^{1}H NMR over a period of 10 hours. The results are plotted in Graph 2. As shown in the graph, at around 60% conversion, the desired product **172aa** was being consumed and a new product was being formed. This side product was isolated and fully characterized, and it was found the to be the α,β-unsaturated product **178**.





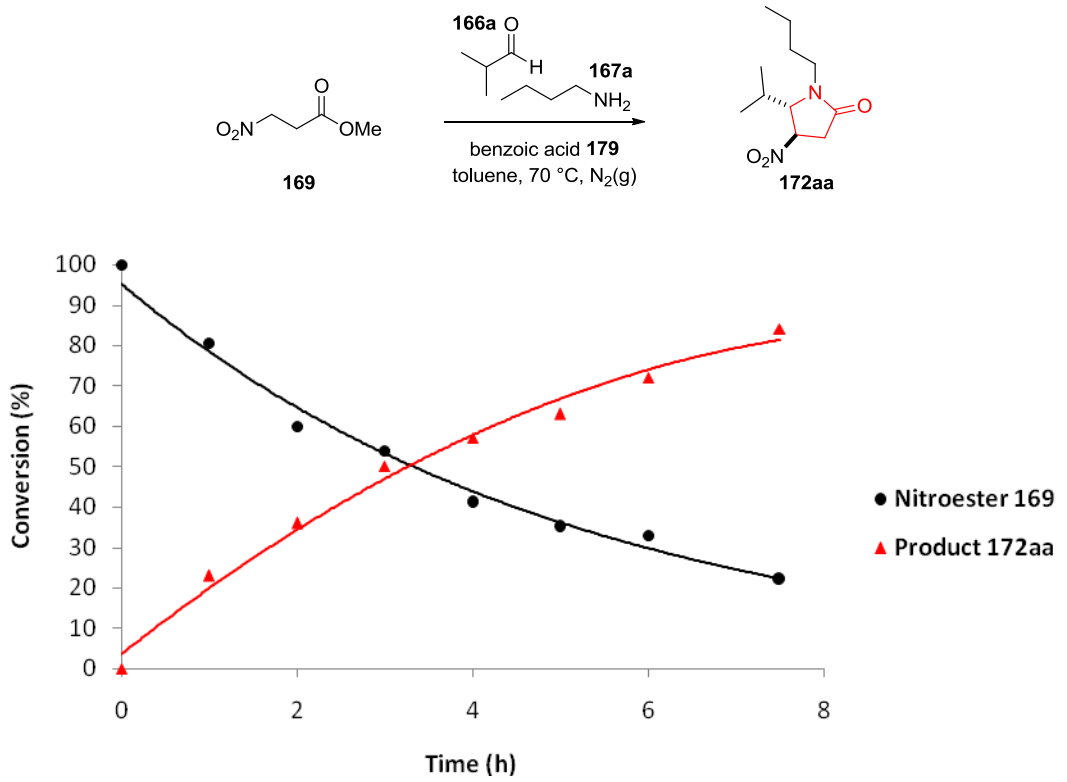
Graph 2 – Observation of the formation of a side product

Presumably, **178** is formed *via* a base catalyzed elimination of the nitro-group of **172aa** and to prevent its formation it was decided to use an acid to buffer the reaction mixture and suppress any base catalyzed reaction pathway. Accordingly, an acid screen was executed.

1.3.3.2 Acid screen

In order to test our hypothesis and see if an acid buffer could suppress the side reaction, an equivalent of benzoic acid **179**, with respect to the amine **167**, was added to the model reaction system mixture. The consumption of methyl 3-nitropropanoate **169** and the formation of desired

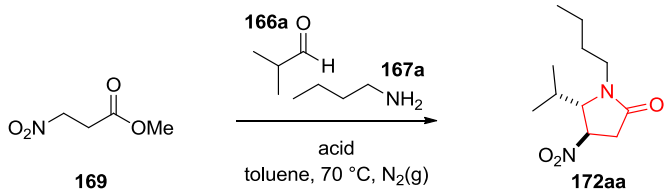
product **172aa**, as a single diastereoisomer, were monitored by ^{1}H NMR spectroscopy and the results are presented in Graph 3.



Graph 3 - Suppression of the side product formation by use of an acid buffer

As shown in Graph 3, buffering the reaction system with benzoic acid **179**, avoided the formation of the side product and the reaction proceeded smoothly up to 85% conversion.

Nevertheless we decided to undertake an acid screen to investigate the efficiency of other acid buffers. The acid screen was performed in the two best solvents (toluene and hexane) to see if the solvent and the acid could have a joined influence on the conversion. It was also decided to try it in water, the least favorable solvent for the reaction, to see if the presence of the acid could influence the efficiency. The reaction was performed with benzoic acid **179**, acetic acid, trifluoroacetic acid, and trichloroacetic acid, and the conversion of each reaction was measured by ^{1}H NMR spectroscopy after an arbitrary period of 6 hours. The results are presented in Table 6.



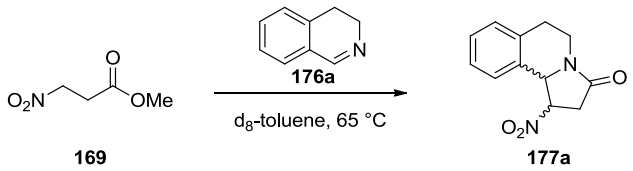
Entry	Acid	Toluene	Hexane	Water
1	Benzoic acid	94%	98%	-
2	Acetic acid	73%	90%	20%
3	TFA	44%	14%	-
4	TCA	68%	50%	-

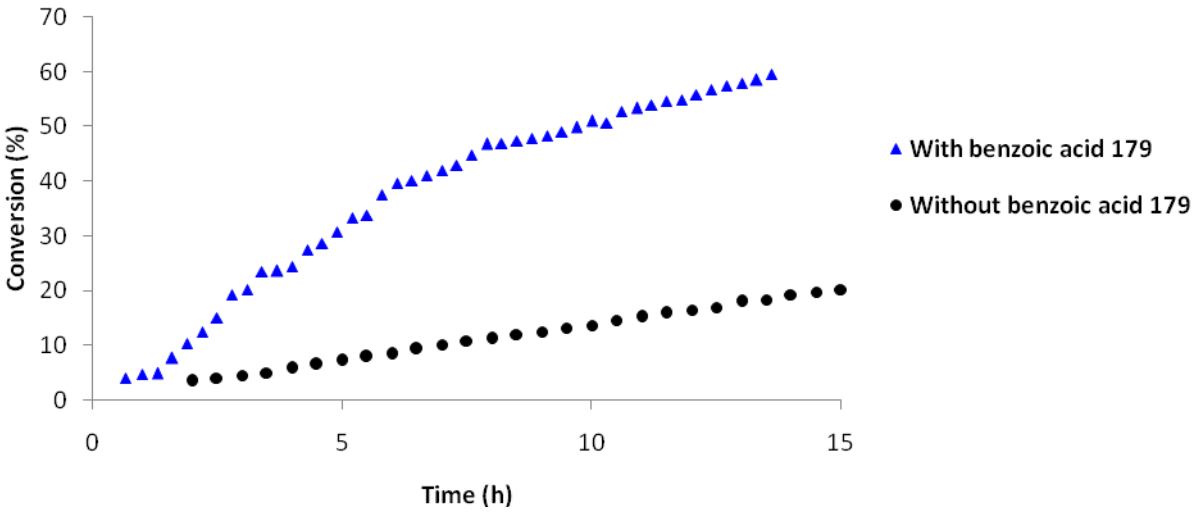
Table 6 – Acid screen

In hexane with acetic acid, TFA or TCA, the product of the elimination of the nitro group, compound **178**, is visible by ^{1}H NMR. This could be a consequence of the fact that the reaction in hexane is not homogeneous and therefore all the reagents are not necessarily in the same phase. The reaction in water still did not show any formation of the product, except when acetic acid was added to the reaction. Even then, the reaction was very messy and low yielding, according to the ^{1}H NMR spectrum. Benzoic acid **179** is incontestably the best acid for the reaction: there were no traces of side product formation and it provided high conversions in toluene and hexane. Benzoic acid **179** was therefore used as an acid buffer in all further studies.

1.3.3.3 Influence of the acid on the kinetics of the reaction

Thanks to the presence of benzoic acid **179** as an acid buffer, the formation of side product **178** was prevented. Furthermore, during these optimisations studies, it appeared that the reaction was proceeding faster in the presence of acid. In order to investigate this observation, the reaction of methyl 3-nitropropanoate **169** with 3,4-dihydroisoquinoline **176a** was performed in deuterated toluene, in the NMR machine at 65 °C. A proton NMR was measured every 15 minutes against an internal standard allowing us to monitor the NMR yield accurately. One reaction was performed with benzoic acid **179** and the other without it. The choice of a preformed cyclic imine was made in order to limit the number of variables in the reaction. The results are depicted in Graph 4.

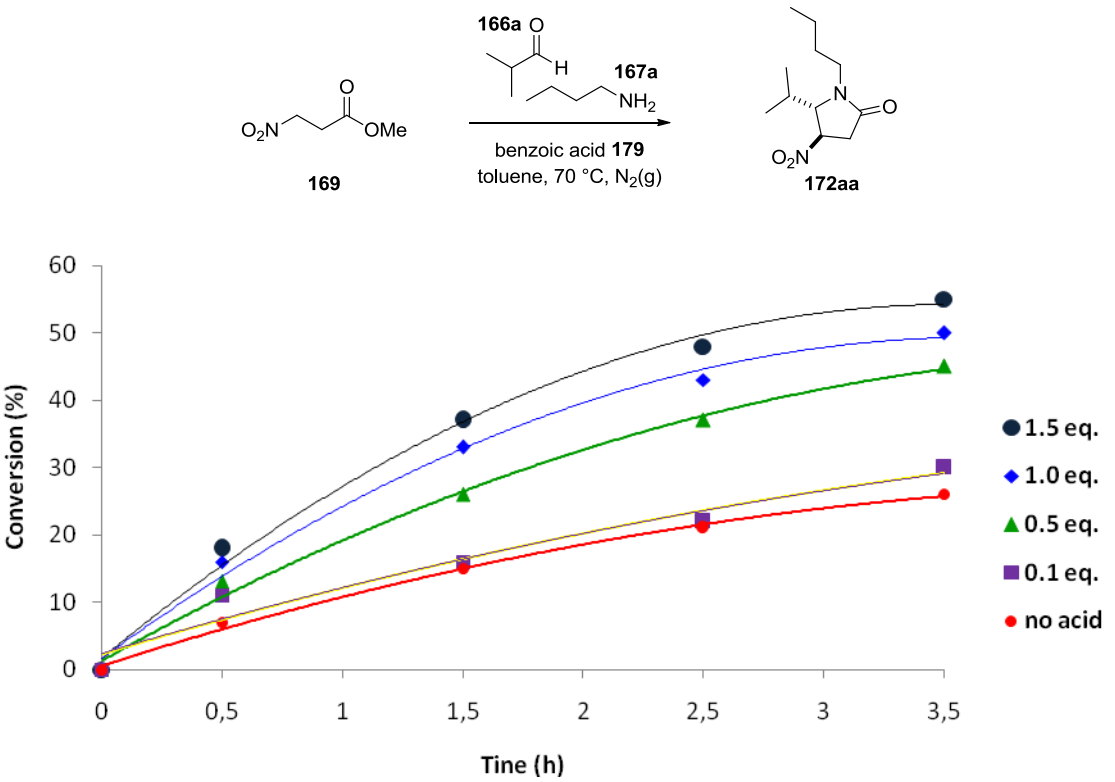




Graph 4 - Benzoic acid 179 acts as a catalyst for the reaction

As shown in Graph 4, the reaction with acid proceeded about 5 times faster than the one without acid, which suggested that benzoic acid **179** acted as a catalyst for the reaction. We also decided to evaluate the effect of the quantity of acid on the reaction rate.

Various reactions were performed at 60 °C, with 1.5 equivalents of amine **167** and aldehyde **166** with respect to the nitroester **169**, and varying equivalents of benzoic acid **179**. The conversion was monitored by ^{1}H NMR spectroscopy at regular time intervals. The results are presented in Graph 5.



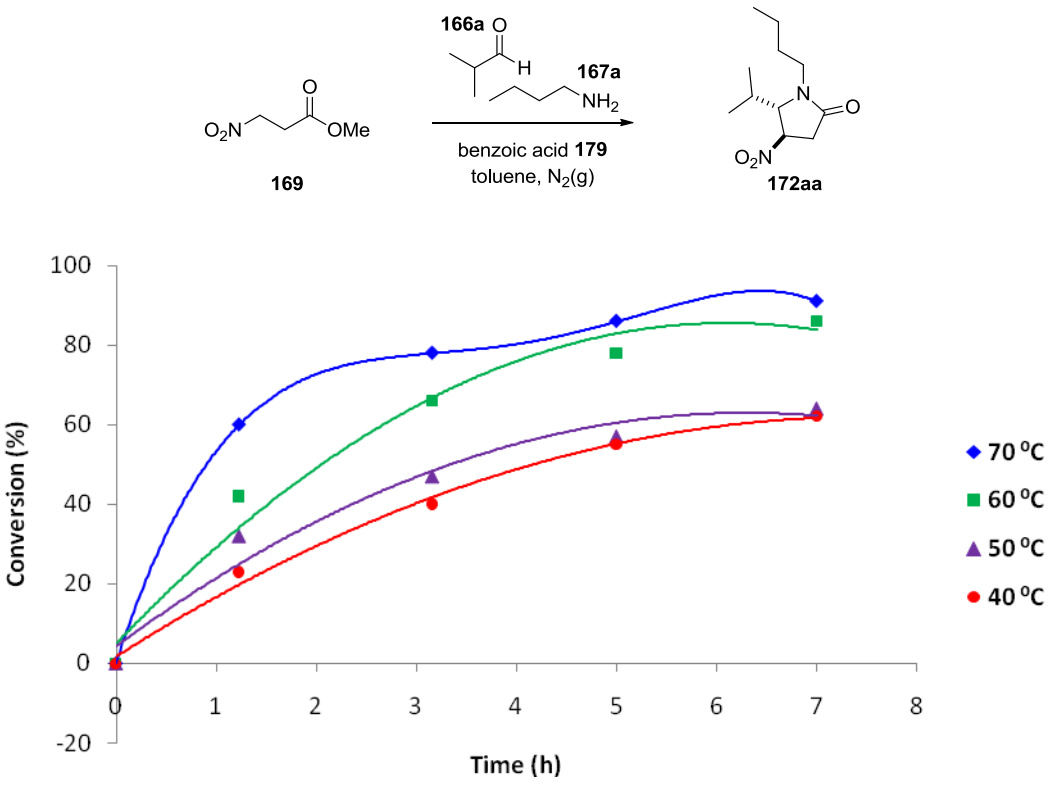
Graph 5 - Influence of the quantity of benzoic acid 179 on the reaction rate

Graph 5 shows that the rate of the reaction increased with increasing equivalents of benzoic acid **179**. Since benzoic acid **179** is readily available and inexpensive, it was decided to use 1 equivalent of acid with respect to the amine **167** (1.5 equivalents with respect to the nitroester **169**) in our reaction for it to proceed at a higher speed.

After examining the influence of the solvent, the atmosphere of the reaction, and after adding an acid buffer, the optimal temperature for the reaction was then investigated.

1.3.4 Temperature screen

A range of reactions were performed with 1.5 equivalents of amine **167**, aldehyde **24** and benzoic acid **179**, with respect to the nitroester **169**, at different temperatures. Results are presented in Graph 6.

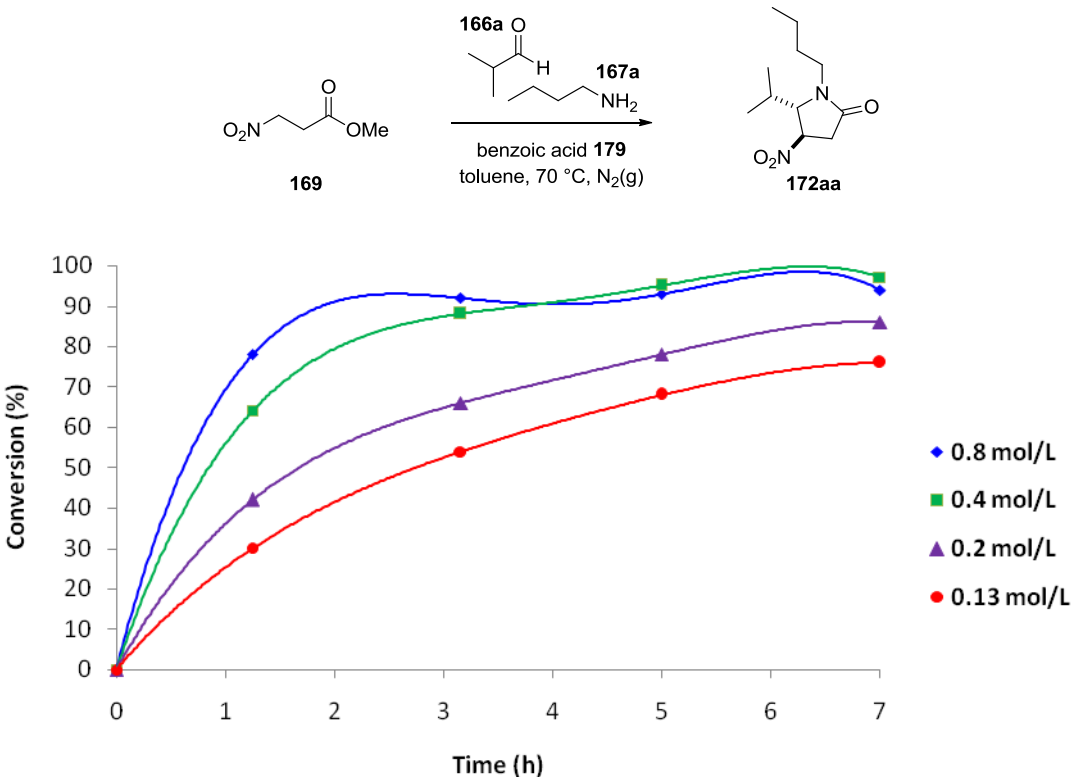


Graph 6 – Influence of the temperature on the reaction

The reaction proceeded at all temperatures between room temperature and reflux in toluene. At room temperature, the reaction proceeded very slowly (40% conversion after 7 days). At reflux, the reaction was quite fast, and was completed within a few hours, but the product had a tendency to decompose under the harsher conditions. At temperatures lower than 60 °C, the reaction was too slow. A temperature of 70 °C was found to be the best compromise between reaction time, reaction efficiency and degradation of the product. In these conditions, 90% conversion to the desired pyrrolidinone **172aa** as a single diastereoisomer was reached in 7 hours. The last parameter to optimise was the concentration of the reagents.

1.3.5 Concentration screen

Several reactions were performed at various concentrations, at 70 °C, with 1.5 equivalents of amine **167**, aldehyde **166** and benzoic acid **179** with respect to the nitroester **169**. The results are presented in Graph 7.



Graph 7 - Optimisation of the concentration

Quite expectedly, the reaction rate increased with increasing concentration. It is worth noting, that the dilution does not have a significant effect on the reactivity and therefore it is possible to change the concentration to better accommodate the scale of the reaction. The desired compound **172aa** was obtained in every reaction as a single diastereoisomer. A concentration of 0.4 mol/L was found to be the best concentration to assure a fast reaction and a convenient volume of solvent to work comfortably on a 100 mg scale.

1.3.6 Work-up screen

Finally, we investigated various ways of working-up the reaction. The first reactions performed were purified directly by flash column chromatography. Unfortunately, benzoic acid **179** has a tendency to "streak" on the column and was always found as a contaminant in the final product. It was decided to proceed with an aqueous basic work-up prior to the column to remove the acid from the reaction mixture. Several bases were tried: saturated aqueous $NaHCO_3$ (pH = 8.5-9), 1M aqueous K_2CO_3 (pH = 13), 1M aqeous NaOH 1M (pH = 14), and 5% aqueous Na_2CO_3 (pH = 11). All of the work up conditions

that were trialed successfully removed benzoic acid **179** from the reaction mixture, but the aqueous work up with 1M potassium carbonate provided the cleanest crude product.

1.3.7 Optimal conditions

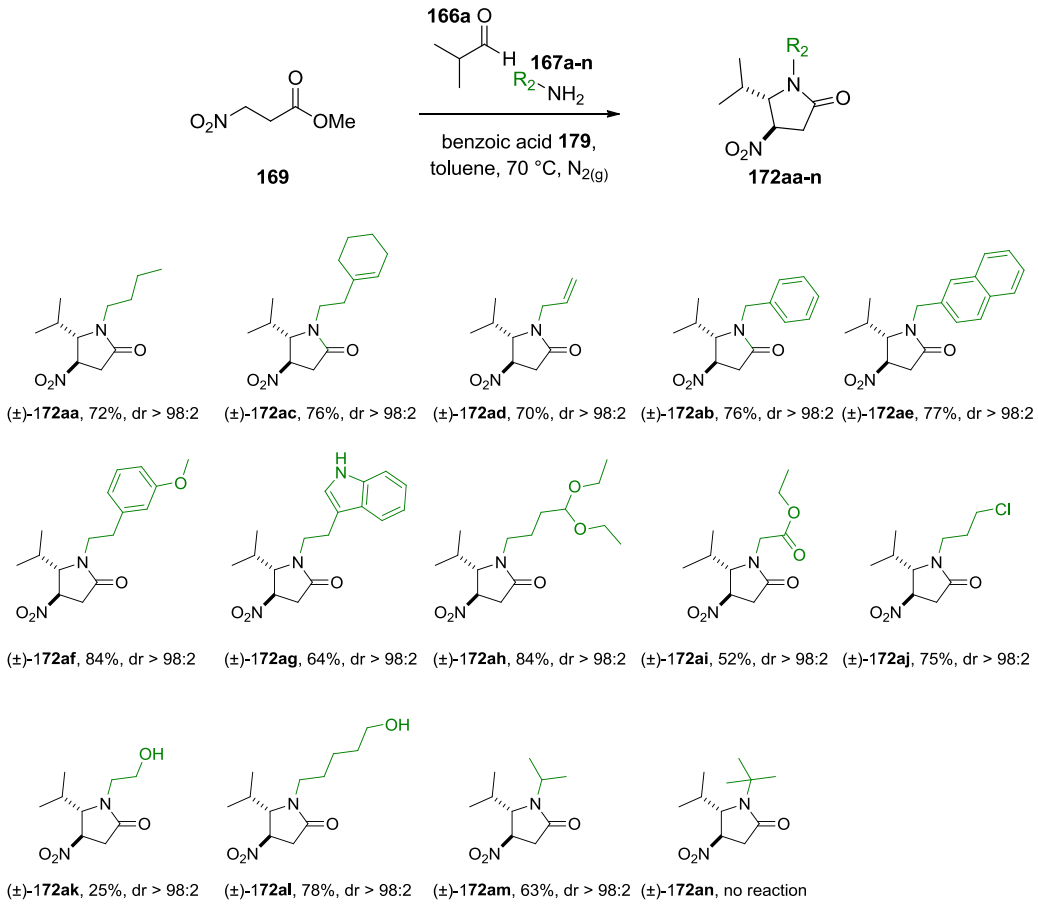
The optimal reaction conditions were found to be the following: 1 equivalent of nitroester **169**, 1.5 equivalents of amine **167**, aldehyde **166** and benzoic acid **179**, in toluene (c= 0.4 mol/L). The reaction vessel had to be sealed and the mixture was pumped/filled three times with nitrogen. The reaction was stirred at 70 °C under an atmosphere of nitrogen and the conversion was monitored by TLC. Upon completion, toluene was evaporated and the residue taken up in dichloromethane. The organic layer was washed three times with 1M aqueous potassium carbonate, dried over sodium sulfate, and then concentrated *in vacuo* to yield the crude desired product **172**. Purification was achieved by flash column chromatography.

1.4 Scope of the reaction with acyclic imines

With optimal reaction conditions in hand, we probed the scope of the reaction with respect to the aldehyde **166**, to the amine **167** and also to preformed cyclic imines **176**.

1.4.1 Scope with respect to the amine 167

With respect to the amine **167**, 13 pyrrolidinones were synthesized in a very good average yield of 69%, from 25% to 84% (Scheme 54). In all cases only a single diastereoisomer was observed by ^{1}H NMR spectroscopy of the crude material. The amines used were all primary amines ranging from linear (**167a**) to sterically hindered (**167m** and **167n**), and bearing various functional group such as ester (**167i**), acetal (**167h**), halide (**167j**), alcohols (**167k** and **167l**) and heterocycle (**167g**).

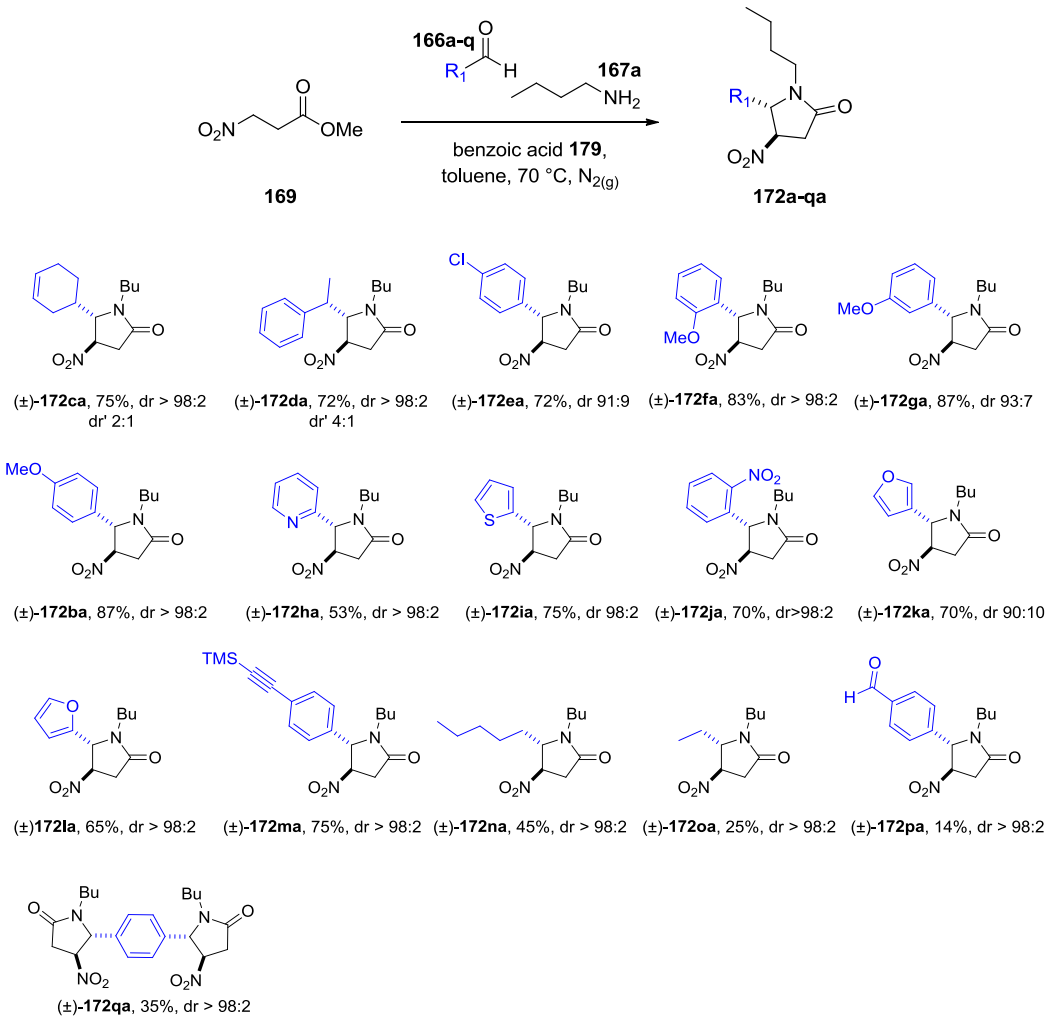


Scheme 54 - Scope of the reaction with respect to the amine 167

It is worth noting that the reaction is sensitive to steric bulk. With a non-bulky linear amine, such as butylamine (**167a**), the reaction proceeds smoothly in 72% yield. With isopropylamine (**167m**), the yield is reduced to 63% and no reaction was observed when ^{t}butylamine (**167n**) was used. A possible explanation for this observation will be given in chapter 5.

1.4.2 Scope with respect to the aldehyde 166

In order to probe the scope of the reaction with respect to the aldehyde **166**, 16 pyrrolidinones were synthesised in a good average yield of 62%. Various aldehydes **166** were used ranging from aliphatic to aromatic (Scheme 55).



Scheme 55 - Scope of the reaction with respect to the aldehyde 166

Aliphatic aldehydes gave excellent diasrereocontrol, only a single diastereomer could be detected in the crude ^{1}H NMR with good yields (products **172aa**, **172ca** and **172da**). Non-branched aldehydes (products **172na** and **172oa**) gave a lower yield, presumably due to aldol side reaction. Aromatic and heteroaromatic aldehydes ranging from electron-rich (product **172ba**) to electron-poor (product **172ja**) and substituted at different positions (products **172fa**, **172ga** and **172ba**) gave excellent yields and good diastereocontrol. In some cases, the minor diastereomer could be observed by crude ^{1}H NMR and was separable by standard column chromatography to give **172** as single diastereomers with the exception of **172ka** which was obtained with a dr of 90:10.

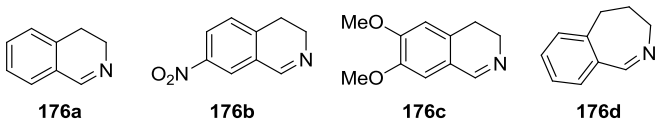
1.5 Extension of the reaction to cyclic imines 176

1.5.1 Synthesis of fused polycyclic pyrrolidinones 177

According to the solvent screen and preliminary studies, the preformed cyclic imines **176** have a similar reactivity to acyclic ones **168**, but they lead to a lower degree of diastereoselectivity. Four cyclic imines (**176a-d**) were synthesized (Figure 7) and reacted with methyl 3-nitropropanoate **169** in the conditions previously optimised for the nitro-Mannich / lactamisation cascade.

A range of six and seven membered ring imines **176a-d** (Figure **7**) were prepared according to literature procedures.

176a[66] and **176c**[67] were made in two steps, respectively from phenylethylamine and dimetoxyphenylethylamine *via* a Bischler-Napieralski reaction. A nitration of **176a** gave **176b**[68] in one step. **176d**[69] was synthesised in three steps from α-tetralone.

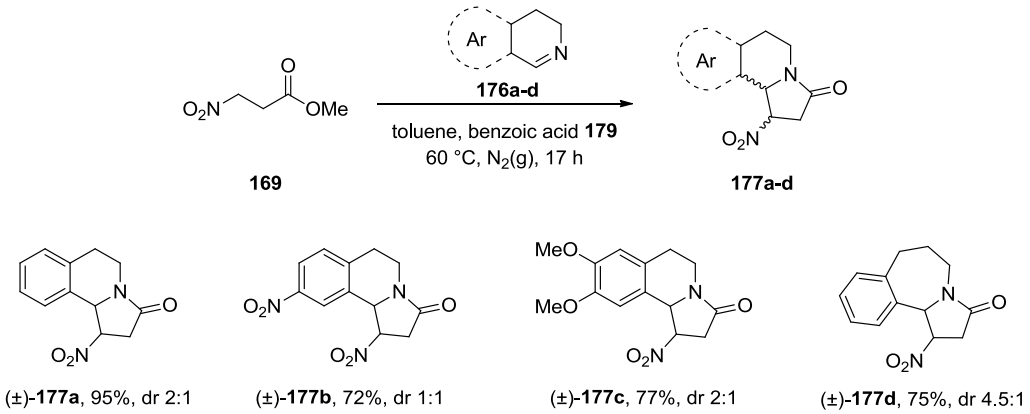


176a 176b 176c 176d

Figure 7 – Cyclic imines 176a-d

Extension of the methodology to cyclic imines allowed the formation of polycyclic pyrrolidinone derivatives **177a-d** (Scheme 56). Imines **176a-d** were reacted with methyl-3-nitropropanoate **169** in toluene with benzoic acid at 70 °C.

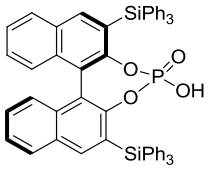
[66] Eliott, M. C.; Williams, E. *Org. Biomol. Chem.* **2003**, *1*, 3038.
[67] Warrener, R. N. *Tetrahedron* **1998**, *54*, 7485.
[68] Venkov, A. P.; Statkova-Abeghe, S. *Synth. Comm.* **1996**, *26*, 127.
[69] (a) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem*. **1996**, *39*, 3539. (b) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett*. **2008**, *10*, 4267.



Scheme 56 – Fused polycyclic pyrrolidinones 177a-d

The reactivity was similar to those of aliphatic imines **168** and the products were formed in excellent yields. However, a lower diastereoselectivity was observed in all cases with crude diastereomeric ratios ranging from 1:1 to 4.5:1.

Interestingly, as we were investigating an enantioselective version of the nitro-Mannich / lactamisation cascade (Chapter 4), it was found that replacing benzoic acid **179** for chiral phosphoric acid **180** (Figure 8) significantly increased the diastereocontrol. This required further investigation.



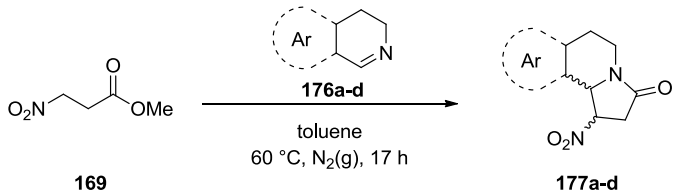
(*R*)-180

Figure 8 – (*R*)-3,3'-triphenylsilyl-binolphosphoric acid 180

1.5.2 Attempts at improving the diastereocontrol of the reaction with cyclic imines 176

1.5.2.1 Influence of the acid on the diastereocontrol

First, a quick screen was executed to assess the effect of the nature of the acid on the diastereocontrol. Every imine **176a-d** was subjected to the reaction in absence of acid, with benzoic acid **179** (1 equivalent with respect to the imine **176**) and with a chiral phosphoric acid **180** (10 mol%). The results are presented in Table 7.

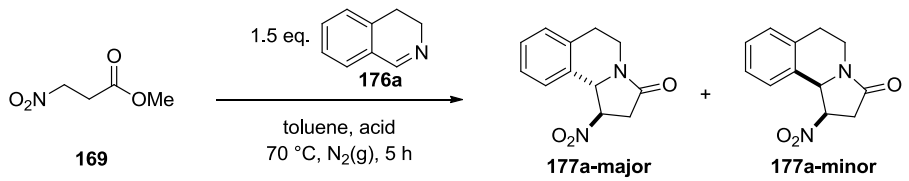


Entry	Imine	Acid	dr
1	**176a**	-	4.5:1
2	**176a**	Benzoic acid **179** (1 eq)	2.0:1
3	**176a**	**Phosphoric acid 180** (0.1 eq)	**14.0:1**
4	**176b**	-	2.8:1
5	**176b**	Benzoic acid **179** (1 eq)	1.0:1
6	**176b**	**Phosphoric acid 180** (0.1 eq)	**7.5:1**
7	**176c**	-	2.0:1
8	**176c**	Benzoic acid **179** (1 eq)	2.0:1
9	**176c**	**Phosphoric acid 180** (0.1 eq)	**5.0:1**
10	**176d**	-	4.5:1
11	**176d**	Benzoic acid **179** (1 eq)	4.5:1
12	**176d**	**Phosphoric acid 180** (0.1 eq)	**7.0:1**

Table 7 - Acid screen to probe the diastereocontrol

Table 7 shows that the diastereocontrol depends strongly on the acid used in the reaction. In the presence of benzoic acid **179** (1 equivalent with respect to the imine **176**), we obtained diastereomeric ratios ranging from 1.0:1 to 4.5:1. In absence of acid, the diastereomeric ratios were comparable to those with benzoic acid **179** (entries 7 and 10) or doubled (entries 1 and 4). The best results were found when using 10 mol% of phosphoric acid **180** with diastereomeric ratio ranging from 5:1 to 14:1.

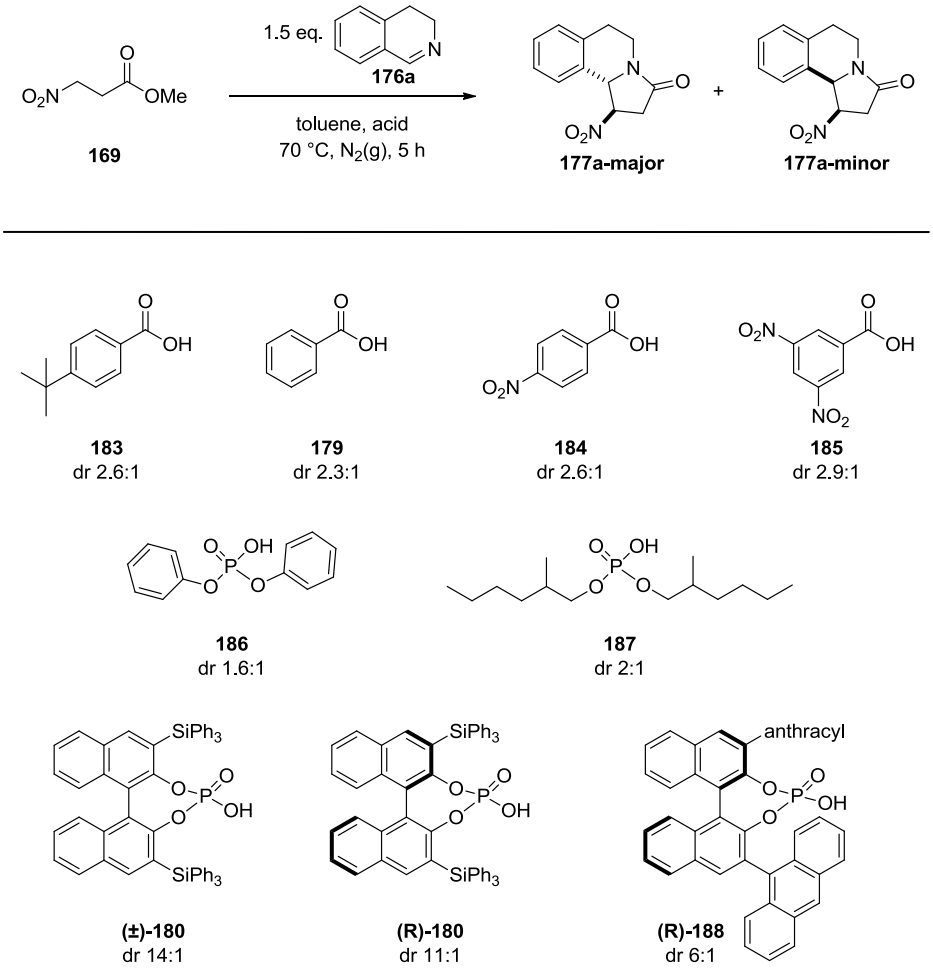
In order to see if the strength of the acid had any effect on the diastereocontrol, the reaction was repeated with three acids of different pKa: benzoic acid **179** (pKa = 4.2), *para*-toluenesulfonic acid **181** (pKa = -6.5) and thiophenol **182** (pKa = 6.6) (Table 8).



Entry	Acid	Conversion	dr (major/minor)
1	Benzoic acid **180**	100%	2:1
2	pTSA **181**	-	-
3	Thiophenol **182**	traces	-

Table 8 – Influence of acids on the diastereocontrol

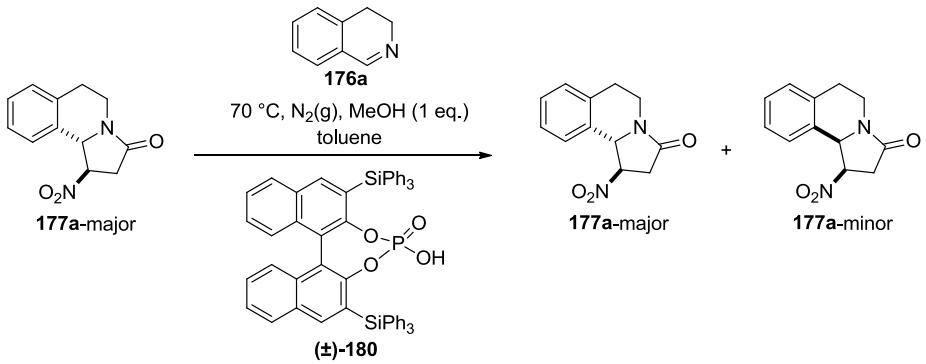
Unfortunately, in the presence of *p*TSA **181** or thiophenol **182** the reaction did not proceed. Another screen was undertaken (Scheme 57), using aromatic carboxylic acid with various substituents (**179**, **183**, **184** and **185**) to tweak the pKa and different phosphoric acids, both achiral and chiral (**186**, **187**, **180** and **188**). The reactions were stopped after an arbitrary period of 5 hours and the diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude mixture.



Scheme 57 – Influence of the nature of the acid on the diastereomeric ratio

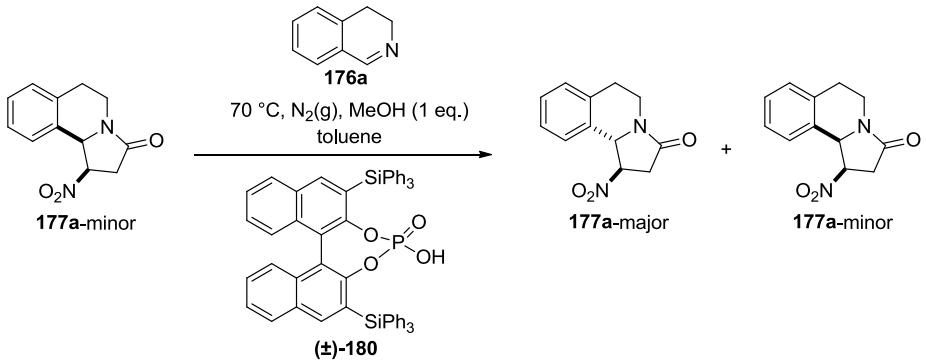
As seen in Scheme 57, the diastereoisomeric ratios measured for the reactions with the aromatic carboxylic acid (**179**, **183**, **184** and **185**) were very similar (within experimental error) and therefore it does not seem that the strength of the acid plays an important role in controlling the degree of diastereoselectivity. Interestingly, results obtained with the phosphoric acids (**180** and **186-188**) suggested that the shape of the acid influences greatly the diastereocontrol with diastereomeric ratios varying from 1.6:1 to 14:1.

It seemed that the nature of the acid had a great influence on the diastereocontrol. However it was not clear whether the acid played a role during the reaction or after the product was formed (through equilibration). Accordingly **177a**-major and **177b**-minor were separated by flash column chromatography and submitted separately to simulated reaction conditions: 10 mol% of chiral phosphoric acid **180**, 1 equivalent of methanol (formed as a product of the lactamisation), and various equivalents of imine **176a** (Table 9 and Table 10). The diastereomeric ratio of each reaction was measured by ^{1}H NMR spectroscopy after 7 hours and 48 hours.



Entry	Acid 180	Imine 176a	Time (h)	dr (major/minor)
1	10 mol%	-	7h	50:1
2	10 mol%	-	48h	50:1
3	10 mol%	0.5 eq	7h	30:1
4	10 mol%	0.5 eq	48h	10:1
5	10 mol%	1.0 eq	7h	25:1
6	10 mol%	1.0 eq	48h	6:1
7	10 mol%	1.5 eq	7h	22:1
8	10 mol%	1.5 eq	48h	5.5:1

Table 9 – Assessing the epimerisation potential of 177a-major

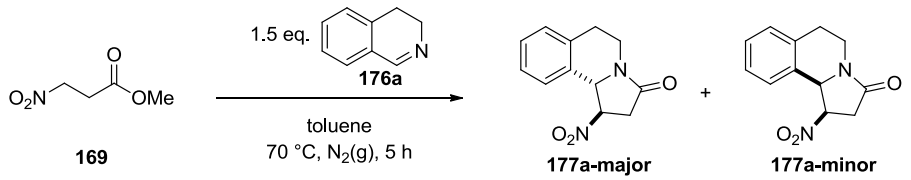


Entry	Acid 180	Imine 176a	Time (h)	dr (major/minor)
1	10 mol%	-	7h	1:4.5
2	10 mol%	-	48h	1:3.0
3	10 mol%	0.5 eq	7h	1:6.0
4	10 mol%	0.5 eq	48h	1:2.4
5	10 mol%	1.0 eq	7h	1:3.5
6	10 mol%	1.0 eq	48h	1:1.0
7	10 mol%	1.5 eq	7h	1:3.5
8	10 mol%	1.5 eq	48h	1:1.0

Table 10 – Assessing the epimerisation potential of 177a-minor

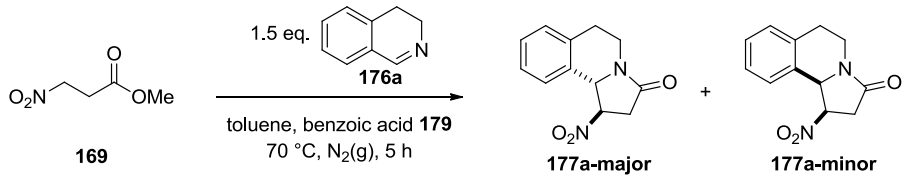
As shown in Table 9 and Table 10, an epimerisation post cyclisation is possible as equilibration happened in all the reactions performed, with the exception of entries 1-2, Table 9. Also, the epimerisation process was more efficient with increasing amounts of imine **176a** present in the reaction. It is worth noting that the equilibration process is slow compared to the time of the reaction. Indeed, the reaction proceeded to completion in about 10 hours and after 48 hours **177a**-minor had only epimerized to a diastereomeric ratio of 1:1.

Finally, two reactions, one without acid and one with benzoic acid, were followed over time until they reached full conversion. The conversion and the diastereomeric ratio at a given time were measured by ^{1}H NMR spectroscopy and the results are reported in Table 11and Table 12.



Entry	Reaction time (h)	Conversion	dr (major/minor)
1	3 h	traces	-
2	18 h	27%	6.5:1
3	28 h	34%	6:1
4	40 h	50%	5.8:1
5	48 h	60%	4.6:1
6	72 h	100%	4.5:1
7	96 h	100%	2.6:1
8	120 h	100%	2:1

Table 11 – Reaction without acid: erosion of the diastereomeric ratio overtime



Entry	Reaction time	Conversion	dr (major/minor)
1	1 h	74%	2.2:1
2	2 h	81%	2.0:1
3	3 h	85%	2.0:1
4	7 h	93%	2.0:1
5	24 h	100%	2.0:1

Table 12 – Reaction with benzoic acid: dr constant overtime

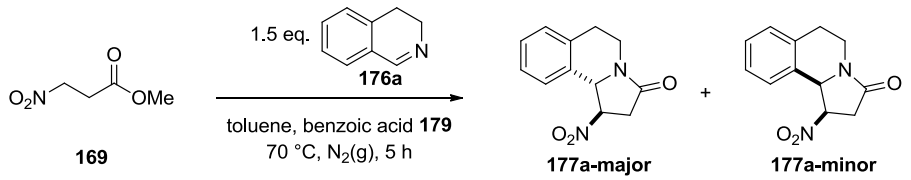
The results reported in Table 11 and Table 12 are really important and provide, combined with previous observations, a strong evidence to explain the origin of the diastereocontrol. In the absence of acid (Table 11) the diastereomeric ratio was found to vary overtime, from 6:1 to 2:1, whereas in the presence of benzoic acid **179** (Table 12) the diastereomeric ratio remained constant overtime (dr 2:1). This suggests that equilibration to the thermodynamic ratio (2:1) occurs instantly with benzoic acid but the process is much slower in the absence of acid. In the case where we used chiral phosphoric acid **180**, we believed that the high degree of diastereocontrol (14:1 for **177a**) is due to the action of acid **180** which prevents the equilibration pathway and therefore the dr observed is the result of the reaction under kinetic control with little erosion by equilibration *post*-reaction. For acyclic imines, the dr was found to be the same with or without acid (benzoic acid **179** or chiral acid

180) and constant overtime. This suggests that in the case of acyclic imines the thermodynamic product and the kinetic products are the same.

Several parameters, such as the dilution, the temperature and the stoichiometry of the reagents were also tested to evaluate their influence on the diastereoselectivity. Since benzoic acid **179** is cheap and commercially available unlike the chiral phosphoric acid **180**, the rest of the optimization studies were performed with benzoic acid **179**.

1.5.2.2 Influence of the dilution on the diastereocontrol

In order to assess the influence of the dilution on the diastereocontrol, the reaction was set up at various concentrations and the diastereomeric ratios were measured by ^{1}H NMR spectroscopy on the crude mixture upon completion of the reaction (Table 13).



Entry	Volume	Concentration	dr (major/minor)
1	0.5 mL	0.38 mol/L	2.5:1
2	1.0 mL	0.19 mol/L	2.2:1
3	1.5 mL	0.12 mol/L	2.1:1
4	3.0 mL	0.06 mol/L	1.9:1
5	5.0 mL	0.04 mol/L	1.8:1

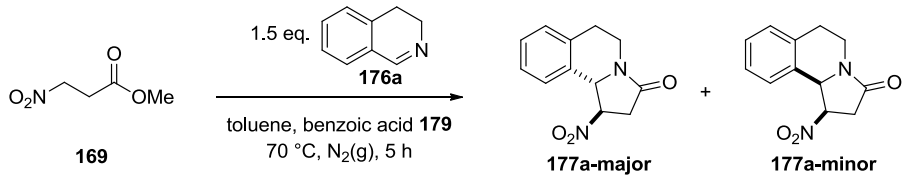
Table 13 – Influence of the dilution on the diastereocontrol

As shown in Table 13, the diastereomeric ratio decreases with increasing dilution with values going from 2.5:1 at 0.38 mol/L (entry 1) to 1.8:1 at 0.04 mol/L (entry 5). Nevertheless, the effect of dilution is very moderate.

1.5.2.3 Influence of the temperature on the diastereocontrol

Then, we investigated the influence of the temperature on the diastereoselectivity. The reaction was then run at various temperatures, ranging from room temperature to 110 °C, and the diastereomeric

ratios were measured by ^{1}H NMR spectroscopy on the crude mixture upon completion of the reaction (Table 14).



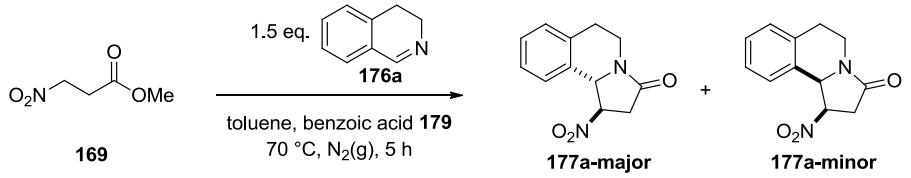
Entry	Temperature	dr (major/minor)
1	RT	1.4:1
2	30 °C	1.5:1
3	55 °C	1.9:1
4	70 °C	2.0:1
5	90 °C	2.2:1
6	Reflux (110 °C)	2.4:1

Table 14 – Influence of the temperature on the diastereocontrol

As shown in Table 14, the diastereomeric ratio increased with the temperature, from 1.4:1 at room temperature (entry 1) to 2.4:1 at 110 °C in refluxing conditions (entry 6). The temperature has a greater effect on the diastereocontrol than the dilution, but it remains moderate.

1.5.2.4 Influence of the stoichiometry of the reagents on the diastereocontrol

The effect of the stoichiometry of the nitroester **169** and the imine **176a** were probed respectively. Reactions were set up with various quantities of both starting materials, and the diastereomeric ratios were measured by ^{1}H NMR spectroscopy on the crude mixture upon completion of the reaction (Table 15).



Entry	Nitroester 169	Imine 176a	dr (major/minor)
1	1.0 eq	3.0 eq	2.2:1
2	1.0 eq	10.0 eq	2.2:1
3	1.5 eq	1.0 eq	1.4:1
4	3.0 eq	1.0 eq	2.0:1

Table 15 – Influence of the stoichiometry on the diastereocontrol

As seen in Table 15, the stoichiometry of both the nitroester **169** and the imine **176a** do not have a significant influence on the diastereoselectivity.

1.5.2.5 Conclusion on the diastereocontrol

In summary, the diastereomeric ratio is not significantly affected by the stoichiometry of the reagents, the concentration, the temperature of the reaction and it remained constant throughout the progression of the reaction. Only changing benzoic acid **179** for chiral phosphoric **180** led to a strong increase in the diastereoselectivity, and we believed that chiral phosphoric acid blocks the thermodynamic equilibration pathway thus leading to the kinetic ratio of products.

1.6 Elucidation of the stereochemistry

1.6.1 For pyrrolidin-2-ones 172

The stereochemistry of the major, and in most cases only, diastereomer obtained was unambiguously determined by single crystal X-ray analysis of compound **172ia** (Figure 9). By comparison of the ^{1}H NMR coupling constants, the stereochemistry of the other compounds (**172aa** to **172qa** and **172an**) was assigned by analogy. In each case, the nitro group of the major diastereomer is in a *trans* relationship with the R group of the aldehyde, to minimize steric repulsion.

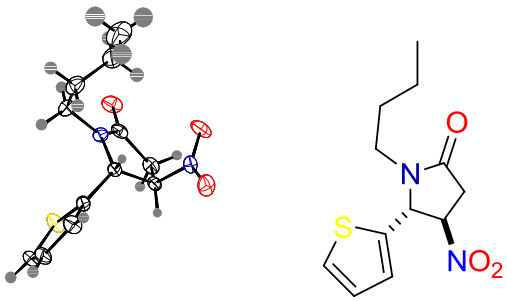


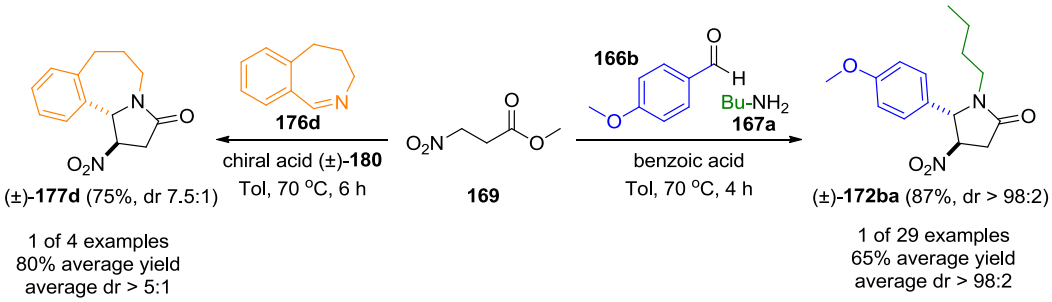
Figure 9 – Crystal structure of 172ia

1.6.2 For fused polycyclic pyrrolidinones 176a-d

The stereochemistry of the major and minor diastereoisomer of **177a-d** was achieved by nOe experiment on **177a**-major and **177a**-minor. The stereochemistry of the other compounds (**177b-d**) was assigned by analogy by comparison of the ^{1}H NMR coupling constants.

1.7 Conclusion

In summary, an efficient diastereoselective nitro-Mannich / lactamisation reaction cascade of methyl 3-nitropropanoate **169** with cyclic **176** and acyclic imines **168**. This is the first general method for the direct preparation of 1,3-disubstituted-4-nitropyrrolidin-2-ones. The reaction is easy to perform, broad in scope (both mono- and polycyclic pyrrolidinone derivatives **172** and **177** respectively can be formed) and scalable. It is worth noting that the yield tends to increase with the scale. This multi-component method is particularly valuable to efficiently generate libraries of compounds or to lower the step count of a total synthesis.



Scheme 58 – Summary

CHAPTER 2

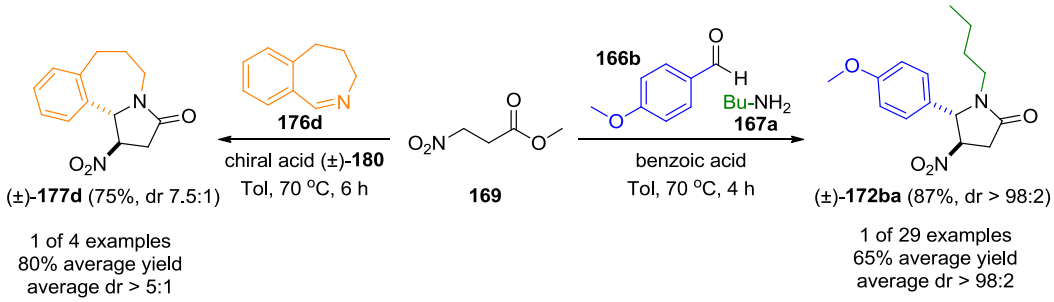
Synthesis of 1,3,5-Trisubstituted-4-nitropyrrolidinones

via

a Nitro-Mannich / Lactamisation Cascade

2.1 Context

In the previous chapter, we described the development of a new methodology for the direct diastereoselective synthesis of *trans* 1,5-disubstituted-4-nitropyrrolidinones **172** *via* a nitro-Mannich / lactamisation cascade between methyl 3-nitropropanoate **169** and an acyclic imine formed *in situ*. The reaction was easy to perform, very broad in scope and the method was extended to the reaction with preformed cyclic imines **176** to access fused tricyclic pyrrolidinones **177** in excellent yields (80% in average) and good diastereocontrol (from 4:1 to 14:1) (Scheme 59).



Scheme 59 – Diastereoselective synthesis of monocyclic and fused tricyclic pyrrolidinones 172 and 177

Considering the abundance of biologically active compounds, such as the HIV inhibitor **189**[70] and the cannabinoid receptor ligand **190**[71], and natural products, such as dysiamide **191**[72] and heliotropamide **192**[73], containing a pyrrolidin-2-one ring substituted in the 3 position (Figure 10), a method of introducing an alkyl substituent alpha to the lactam carbonyl was required.

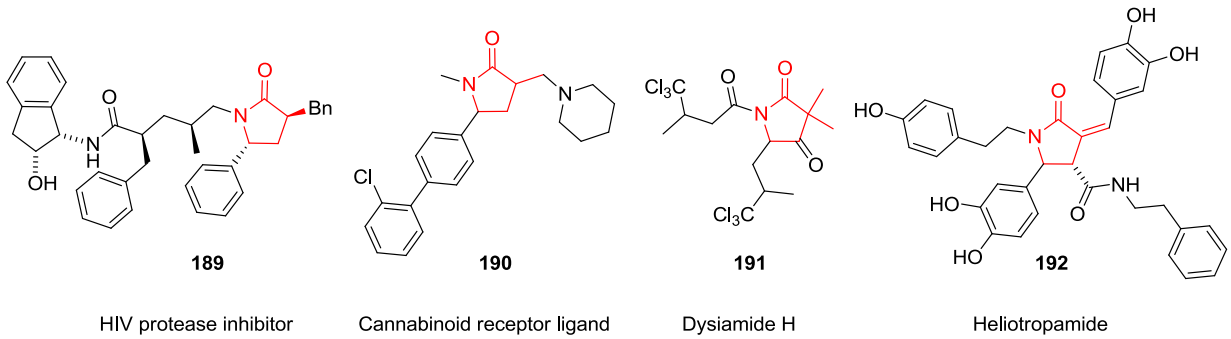
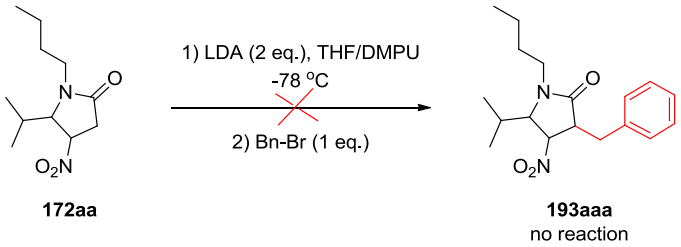


Figure 10 – 3-Substituted pyrrolidin-2-one natural products and biologically active compounds

[70] (a) Kazmierski, W. M.; Andrews, W. C.; Furfine, E. S.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689. (b) Sherrill, R. G.; Andrews, W. C.; Bock, W. J.; Davis-Ward, R. G.; Furfine, E. S.; Hazen, R. J.; Rutkowske, R. D.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 81.
[71] Enz, A.; Feuerbach, D.; Frederiksen, M. U.; Gentsch, C.; Hurth, K.; Müller, W.; Nozulak, J.; Roy, B. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1287.
[72] Sauleau, P.; Retailleau, P.; Vacelet, J.; Bourguet-Kondracki, M.-L. *Tetrahedron* **2005**, *61*, 955.
[73] Guntern, A.; Ioset, J.-R.; Queiroz, E. F.; Sándor, P.; Foggin, C. M.; Hostettmann, K. *J. Nat. Prod.* **2003**, *66*, 1550.

A range of conditions to directly alkylate the previously synthesised pyrrolidin-2-ones **172aa** were attempted but failed to yield any of the desired products **193aaa** and one of them is presented in Scheme 60.

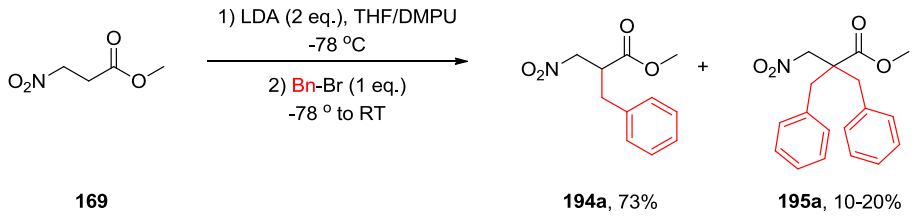


Scheme 60 – Direct alkylation of 172aa alpha to the lactam carbonyl

Accordingly, and in order to circumvent this issue, we decided to investigate an alternative route in which methyl 3-nitropropanoate **169** would be *C*-alkylated *prior* to the nitro-Mannich / lactamisation cascade. In relation to our previous work detailed in chapter 1, this development would raise new issues of reactivity, reaction scope and diastereoselection in the products and as such was a worthy pursuit.

2.2 Proof of principle

Following modified literature procedures, methyl 2-benzyl-3-nitropropanoate **194a** was synthesised in one scalable step from the parent methyl 3-nitropropanoate **169**.[74] The gem-dialkylated compound **195a** was isolated as a side product of the alkylation reaction (Scheme 61).

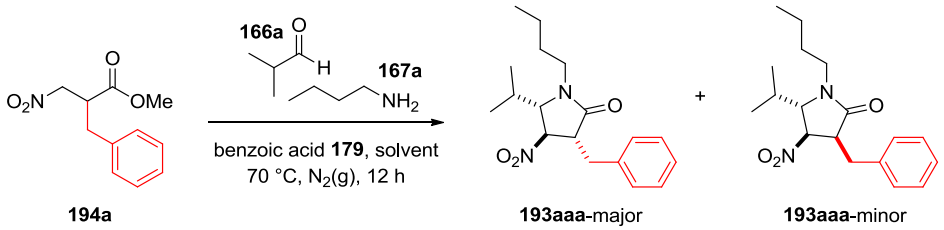


Scheme 61 – Synthesis of 194a *via* direct alkylation of 169 alpha to the carbonyl

With **194a** in hand, a range of preliminary experiments to identify conditions for a nitro-Mannich lactamisation cascade were performed using isobutyraldehyde (1.5 eq), butylamine (1.5 eq) and

[74](a) O'Neil, I. A.; Bhamra, I.; Gibbsons, P. D. *Chem. Commun.* **2006**, 4545. (b) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705.

benzoic acid (1.5 eq) in a range of solvents at 70 °C in sealed vessels for a fixed time of 12 hours (Table 16).

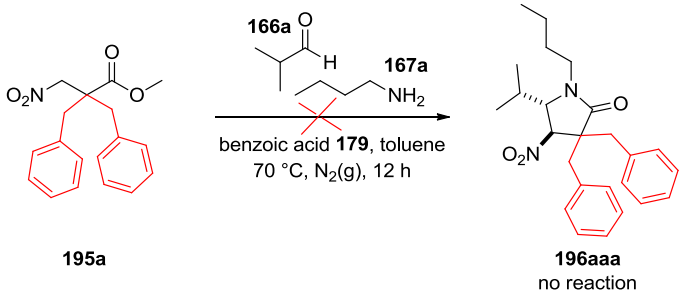


Entry	Solvent	^{1}H NMR yield of 193aaa (%)	dr
1	MeOH	29%	2.5:1
2	EtOAc	62%	3.0:1
3	Et_2O	84%	3.5:1
4	THF	60%	3.5:1
5	Hexane	92%	4.5:1
6	Toluene	93%	4.5:1

Table 16 – Preliminary conditions screen

Although little product was observed in methanol (entry 1), pleasingly with ethyl acetate, diethyl ether and tetrahydrofuran as solvents (entries 2, 3 and 4), the reactions were efficient and only 2 of the 4 possible diastereoisomers were obtained in moderate to good diastereoselectivities. Further screening revealed hexane and toluene to be optimal with respect to both reaction yield and diastereoselectivity (entries 5 and 6).

Unfortunately, with the sterically hindered gem-dialkylated starting material (**195a**), no reactivity under these conditions in toluene was observed (Scheme 62).



Scheme 62 – Failed attempt at a cascade reaction with gem-dialkylated compound 195a

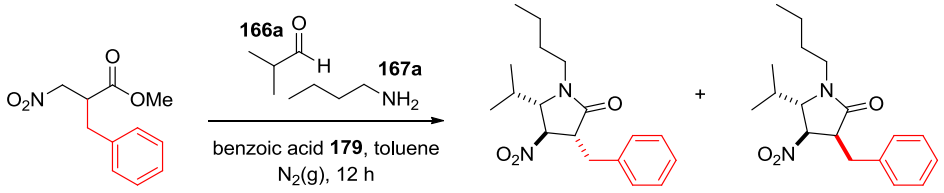
With this proof of principle in hand, various reaction parameters were studied in order to optimise the reaction conditions.

2.3 Optimisation studies

According to the results obtained in the preliminary solvent screen, the nitro-Mannich / lactamisation cascade of substituted nitro-esters proceeds very efficiently (conversion of 93% in toluene). However, the stereocontrol of the newly created stereocenters was moderate and an optimisation study of the reaction parameters was undertaken with the aim of improving the diastereoselectivity.

2.3.1 Temperature screen

The first parameter that was studied in order to optimise the diastereoselectivity of the nitro-Mannich / lactamisation cascade of substituted nitroester **194a** was the temperature. The reaction of nitroester **194a**, isobutyraldehyde **166a**, butylamine **167a** and benzoic acid **179** was performed at various temperatures ranging from room temperature (about 20 °C) to reflux in toluene (about 110 °C). The diastereomeric ratio was measured by ^{1}H NMR spectroscopy on the crude mixture and the results are presented in Table 2.



194a **193aaa**-major **193aaa**-minor

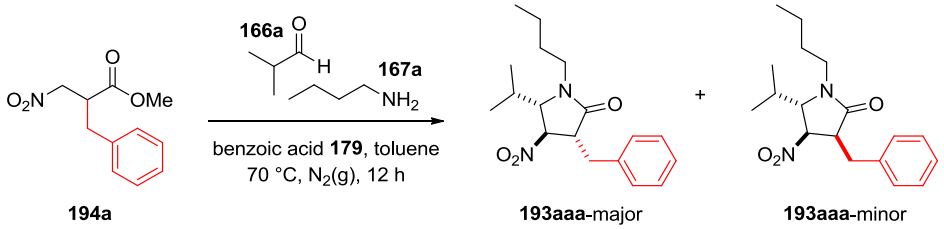
Entry	Temp. (°C)	dr
1	RT	4.5:1
2	30 °C	4.4:1
3	55 °C	4.0:1
4	70 °C	4.5:1
5	90 °C	3.9:1
6	110 °C	4.5:1

Table 17 – Effect of the temperature on the diastereocontrol

The desired pyrrolidinone **193aaa** was formed at all temperatures but the diastereomeric ratio remained unchanged (within experimental error) through the temperature screen.

2.3.2 Concentration screen

Next, we investigated the influence of the dilution on the diastereocontrol. A range of reactions was performed with nitroester **194a**, isobutyraldehyde **166a**, butylamine **167a** and benzoic acid **179** at different concentration in toluene at 70 °C. The diastereomeric ratio was measured by ^{1}H NMR spectroscopy on the crude mixture and the results are presented in Table 18.



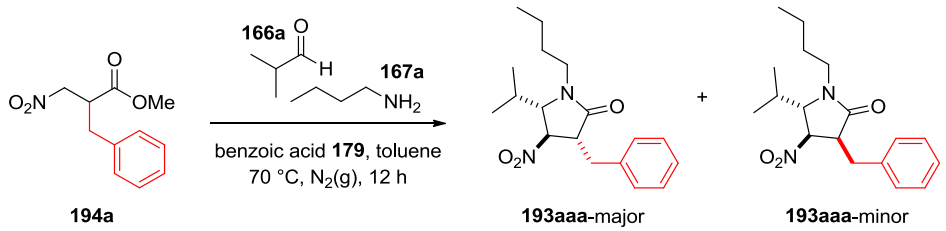
Entry	Concentration (mol/L)	dr
1	neat	3.0:1
2	0.68 mol/L	4.2:1
3	0.34 mol/L	4.5:1
4	0.22 mol/L	4.5:1
5	0.11 mol/L	4.5:1
6	0.05 mol/L	4.6:1

Table 18 – Effect of the concentration on the diastereocontrol

The reaction proceeded at all concentrations even in the absence of solvent. Apart from the reaction under neat conditions (entry 1) which provided a lower diastereocontrol (3:1), the dilution did not have any effect on the diastereoselectivity and the diastereomeric ratio remained constant at 4.5:1.

2.3.3 Stoichiometry of the acid

Then, the effect of the stoichiometry of benzoic acid **179** on the diastereocontrol of the reaction was probed. A range of reactions was performed with nitroester **194a**, isobutyraldehyde **166a** and butylamine **167a** in toluene at 70 °C with various quantities of benzoic acid **179**. The diastereomeric ratio was measured by ^{1}H NMR spectroscopy on the crude mixture and the results are presented in Table 19.



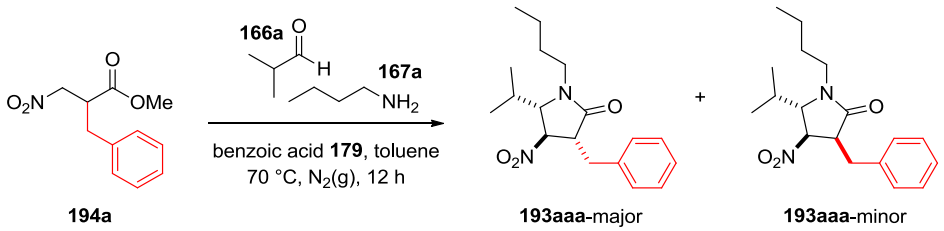
Entry	Benzoic acid (eq)	Time (h)	Conversion (%)	dr
1	-	12 h	18%	6.0:1
2	-	24 h	43%	5.2:1
3	0.1 eq	12 h	56%	5.2:1
4	0.1 eq	24 h	81%	4.5:1
5	1.5 eq	12 h	68%	4.5:1
6	1.5 eq	24 h	100%	4.5:1
7	3.0 eq	12 h	84%	4.5:1

Table 19 – Effect of the stoichiometry of benzoic acid 179 on the diastereocontrol

Each reaction was first sampled after an arbitrary period of 12 hours (entries 1, 3, 5, and 7) and both the conversion and the diastereomeric ratio were measured by ^{1}H NMR spectroscopy. Interestingly, in the absence of benzoic acid **179** or in reactions employing a catalytic amount of benzoic acid **179** (0.1 eq), the diastereoselectivity seemed to be improved at low conversions to 6:1 and 5.2:1 respectively (entries 1 and 3). In order to verify these data, the reactions were allowed to proceed further (43% and 81% conversion respectively) and a second sample was taken after another 12 hours (entries 2, 4 and 6). In both reactions, the diastereomeric ratio had decreased, to 5.2:1 and 4.5:1 respectively (entries 2 and 4) to reach the usual ratio. With 1.5 equivalents and 3.0 equivalents of acid, the diastereoselectivity remained unchanged (4.5:1 dr). It was concluded that the stoichiometry of the acid did not have a significant influence on the diastereocontrol but that maybe it was changing with the advancement of the reaction which would explain the higher ratio obtained in entries 1 and 3.

2.3.4 Diastereomeric ratio over time

In order to know if the diastereomeric ratio was changing over time, a new reaction was set up with nitroester **194a**, isobutyraldehyde **166a**, butylamine **167a** and benzoic acid **179** (1.5 eq) in toluene at 70 °C and the diastereomeric ratio was measured every 5 min for an hour, than after 4 hours, 7 hours and 48 hours. The diastereomeric ratio was measured by ^{1}H NMR spectroscopy on the crude mixture and the results are presented in Table 20.



Entry	Time	dr
1	5 min	-
2	10 min	-
3	15 min	-
4	20 min	-
5	25 min	4.0:1
6	30 min	5.0:1
7	35 min	5.0:1
8	40 min	5.0:1
9	45 min	4.0:1
10	50 min	4.0:1
11	55 min	4.0:1
12	60min	4.5:1
13	4 h	4.5:1
14	7 h	4.5:1
15	48 h	4.5:1

Table 20 – Diasteromeric ratio overtime

For the first 20 minutes, the diastereomeric ratio could not be measured because the conversion to the desired product **193aaa** was too low. Then, between 25 minutes and 48 hours, the diastereomeric ratio remained constant within experimental error.

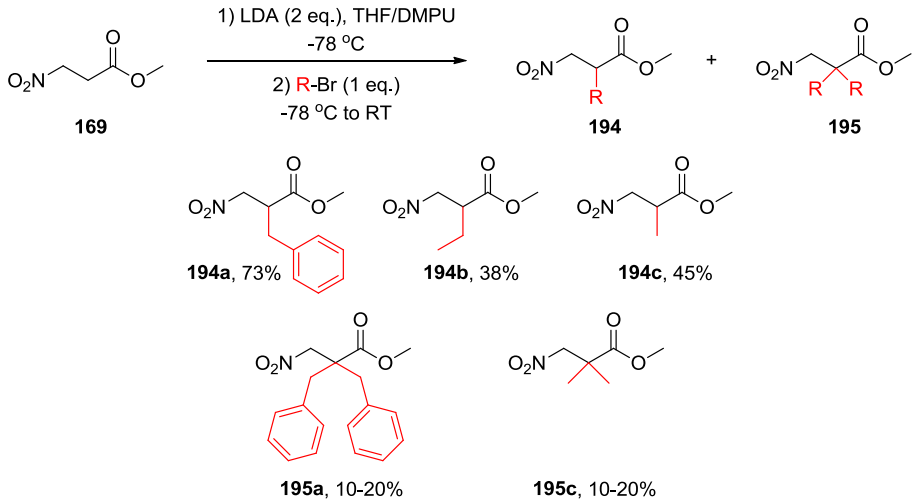
2.3.5 Conclusion

Neither the temperature nor the dilution or the stoichiometry of benzoic acid **179** had any effect on the diastereoselectivity, and the diastereomeric ratio remained constant overtime. The reaction was also performed with chiral phosphoric acid **180** and with various stoichiometry of amine **167** and aldehyde **166** and the diastereomeric ratio was not affected by those changes. With optimal reaction conditions established, only the scope of the reaction and the degree of stereocontrol possible in the formation of the fully substituted pyrrolidin-2-one products **5** remained to be investigated.

2.4 Scope of the reaction

2.4.1 Synthesis of starting material

A range of substituted nitroesters **194** were synthesised following the same procedures used for **194a** (Scheme 63).[74]



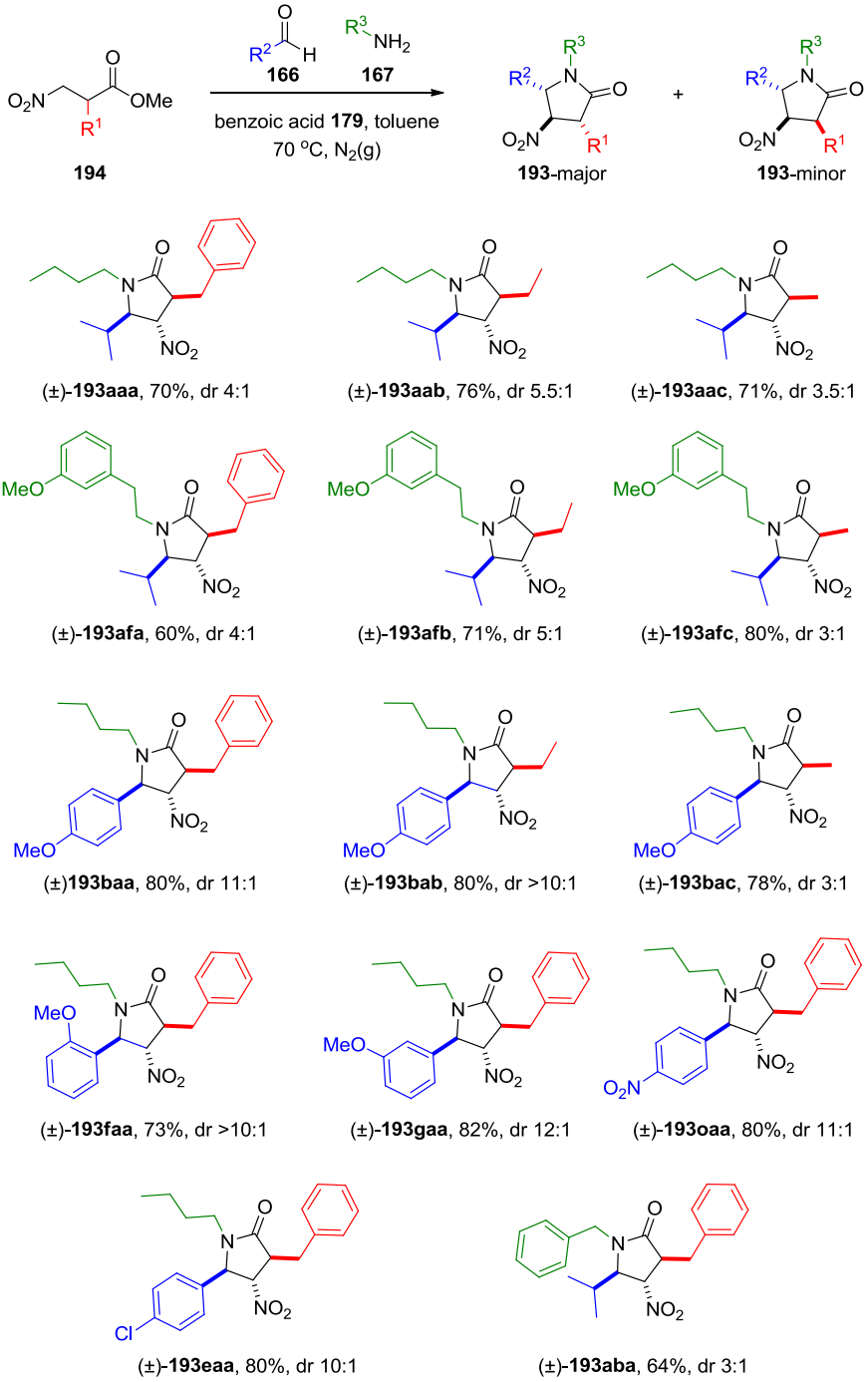
Scheme 63 – Synthesis of methyl 2-alkylated-3-nitropropanoates 6

As seen previously, gem-dialkylated product **195c** was isolated as a side product of the formation of **194c** and as predicted it was unreactive towards a nitro-Mannich / lactamisation cascade.

With nitroester **194a-c** in hand, the scope of the reaction could then be probed.

2.4.2 Preliminary scope

Initially, with nitroesters **194a-c**, we probed the scope of the nitro-Mannich / lactamisation reaction using 1.5 equivalents respectively of amine **167**, aldehyde **166** and benzoic acid **179** in toluene at 70 °C. The results are presented in Scheme 64.



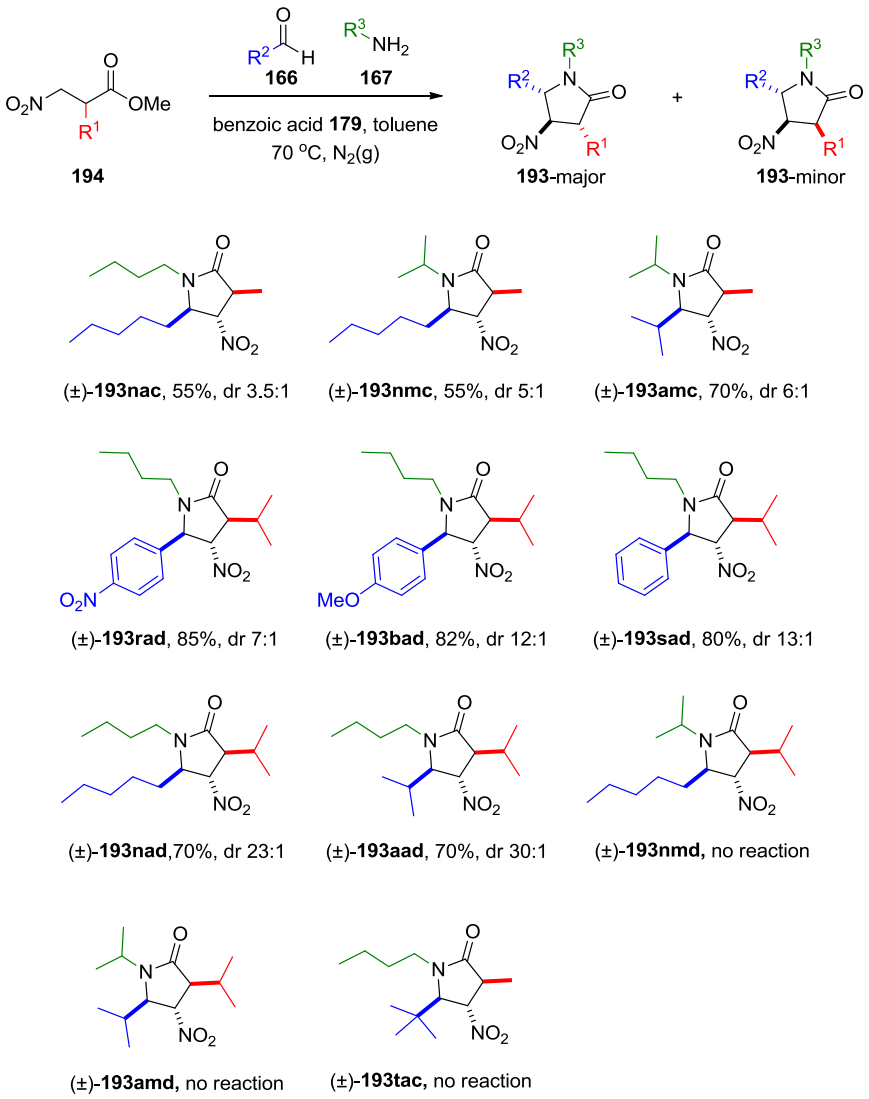
Scheme 64 – Establishing the initial scope of the reaction

The reaction was first performed using isobutyraldehyde **166a** and butylamine **167a**. Pleasingly, mono-substituted alkylnitroesters **194a-c**, all provided the desired products **193aaa**, **193aab** and **193aac**. Reaction yields averaged 73% and moderate to good diastereoselectivities (ranging from 3.5:1 to 5.5:1 dr) were obtained. Substituting butylamine **167a** for 2-(2-methoxyphenyl)ethanamine **167f** gave similar results with isobutyraldehyde (**193afa**, **193afb** and **193afc**). In each case, the 2-methyl substituted nitroester starting material **194c** gave a lower diastereoselectivity than the

analogous benzyl substituted **194a** or ethyl substituted starting material **194b**. Interestingly, when *p*-methoxybenzaldehyde **166b** was employed in the cascade, a significant increase in diastereocontrol was observed. With ethyl and benzyl substituted nitroesters **194b** and **194a** respectively, the diastereoselectivity was greater than 10:1. This high level of diastereocontrol was maintained with ortho (**193faa**), meta (**193gaa**) and para (**193baa**) substitution around the ring and for electron rich, electron poor (**193oaa**) and halide substituted (**193eaa**) rings.

2.4.3 Extended scope

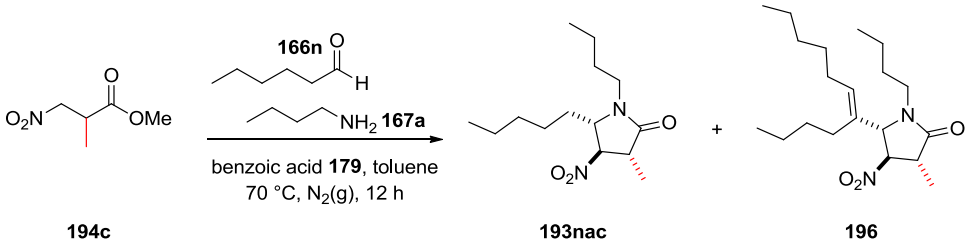
A closer analysis of the data from Scheme 64 suggested that the degree of diastereocontrol varied as a function of the steric demand of the reagents. Accordingly, with the aim of improving the diastereomeric ratio, sterically demanding methyl 2-isopropyl-3-nitropropanoate **194d** was synthesised and another set of pyrrolidinones **193** were synthesised with increasing steric bulk around the ring (Scheme 65).



Scheme 65 – Effect of the steric bulk on the diastereoselectivity

By increasing the steric bulk of the substituents around the ring, it was possible to strongly affect the diastereomeric ratio from 3.5:1 for **193nac** bearing only linear substituents to 30:1 for **193aad** bearing two isopropyl groups in the 3 and 5 positions. Whenever methyl 2-isopropyl-3-nitropropanoate **194d** was used, good to excellent diastereocontrol ranging from 7:1 for **193rad** to 30:1 for **193aad**, was observed. Using the hindered amine, isopropylamine **167m**, also gave rise to improved dr (5:1 for **193nmc** *vs* 3.5:1 for **193nac**), but the reaction was significantly slower and when reacted with 3-isopropylnitroester **194d**, no formation of product was witnessed (**193nmd** and **193amd**). Using ^{t}butyraldehyde **166t** also failed to provide any of the desired pyrrolidinone **193tac**. Further studies to explore the mechanism of the reaction and determine the origin of the stereocontrol will be performed in chapter 5. However it is worth noting that the reaction with linear

aldehydes, such as hexanal **166n**, proceed in lower yields due to the occurance of an aldol side reaction. This was an just an hypothesis in chapter 1, but during the formation of **193nac** we isolated **196** which is the product of an aldol reaction which then underwent a nitro-Mannich / lactamisation cascade (Scheme 66).



Scheme 66 – Evidence of the occurance of aldol side reaction

2.4.4 Extension to the reaction with cyclic imines

Extension of the methodology to cyclic imines **176b** and **176b** (Figure 11) allowed the formation of multicyclic pyrrolidinone derivatives **177**.

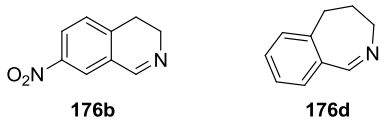
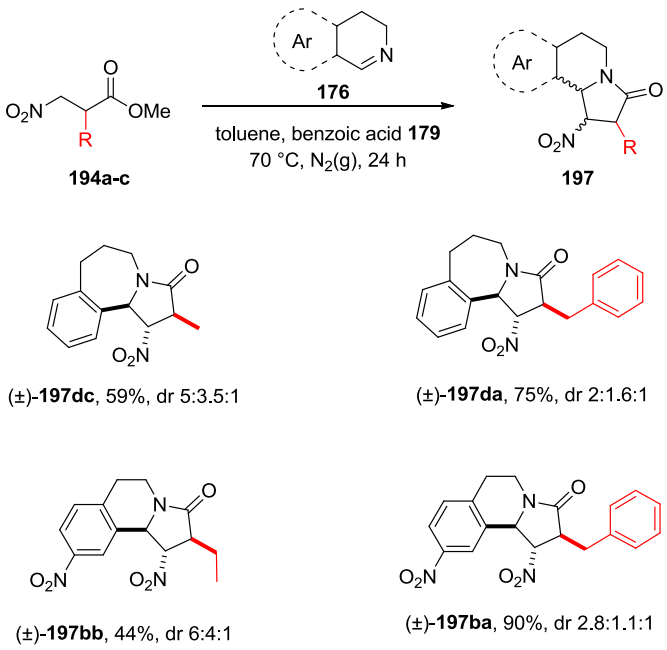


Figure 11 – Cyclic imines 176b and 176d

Imines **176b** and **176d** (Figure 11) were reacted with nitroesters **194a-c** in toluene with benzoic acid **179** at 70 ˚C, and the results are presented in Scheme 67.



Scheme 67 – Synthesis of fused tricyclic pyrrolidinones 197

The products **197** were formed in slightly lower yields and in poor diastereocontrol, and the separation of the diastereomeric products proved to be difficult.

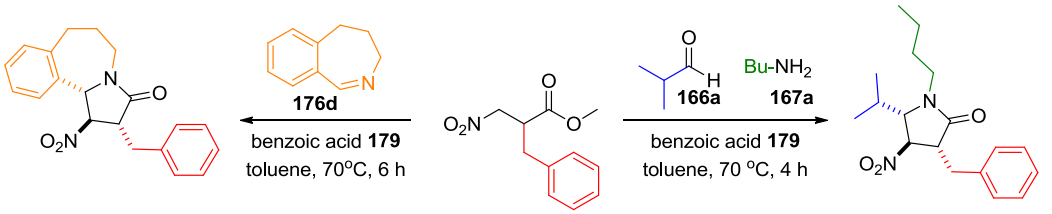
2.5 Stereochemistry

The *trans/trans* relative stereochemistry of the major diastereoisomer was unambiguously determined by single crystal X-ray analysis of compounds **193aaa** and **193oaa**. By comparison of the ^{1}H NMR coupling constants, the stereochemistry of the major diastereoisomer of pyrrolidinones **193** was assigned by analogy. Similarly, the *trans/cis* relative stereochemistry of the minor diastereoisomers of the reaction was assigned by analogy to that of **193aba** which was unambigously determined by single crystal X-ray analysis.

2.6 Conclusion

In summary, an efficient diastereoselective nitro-Mannich / lactamisation reaction cascade of methyl 2-alkyl 3-nitropropanoate **6** with imines generated *in situ* has been developed (Scheme 68). This versatile extension of the work reported in the previous chapter now allows direct, diastereoselective preparation of 1,3,5-trisubstituted 4-nitropyrrolidin-2-one derivatives **193**. The

diastereocontrol was found not to be affected by the reaction parameters (temperature, dilution, stoichiometry and nature of the acid) and to remain constant over time. However, further studies revealed that the diastereoselectivity increased strongly with the steric bulk on the subsituents. The methodology has also been extended to the reaction with cyclic imines **176** to give rise to fused tricyclic pyrrolidinones **197** in good yields but poor diastereoselectivities.



(±)-**197da**
(75%, dr 2:1.6:1)

1 of 4 examples
67% average yield
average dr > 5:1

194a

(±)-**193aaa** (70%, dr 4:1)

1 of 22 examples
73% average yield
dr from 3:1 to 30:1

Scheme 68 – Summary

It is noteworthy that this extension of the nitro-Mannich / lactamisation cascade strongly broadens the scope of the synthesis of pyrrolidin-2-ones.

CHAPTER 3

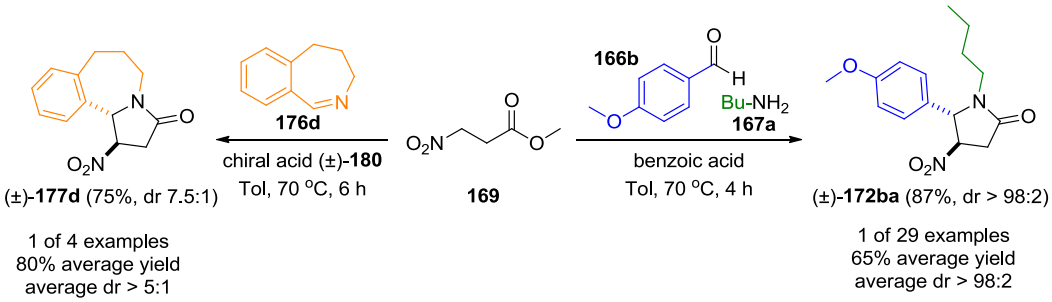
Extension of the Methodologies

and

Synthetic Applications

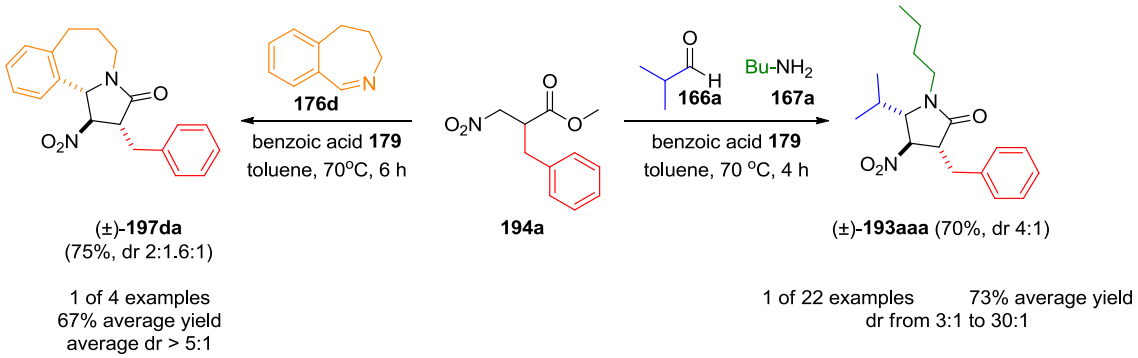
3.1 Context

In the first chapter, the development of a new methodology for the direct and efficient diastereoselective synthesis of *trans* 4-nitropyrrolidinones **172** and **177** *via* a nitro-Mannich / lactamisation cascade between methyl 3-nitropropanoate **169** and an imine formed *in situ* or otherwise was described (Scheme 69).



Scheme 69 – Diastereoselective synthesis of monocyclic 172 and fused tricyclic 177 pyrrolidinones

In the following chapter, this methodology was extended to the reaction with methyl 2-alkylsubstituted-3-nitropropanoate **6** to allow the formation of fully substituted pyrrolidinones **5** and **177e-h** (Scheme 70).



Scheme 70 – Diastereoselective synthesis of fully substituted pyrrolidinones 193 and 197.

In order to extend this work even further, we proposed to investigate the synthesis of pyrrolidinones with others substitution patterns, then to demonstrate their synthetic utility *via* a range of functional group modifications, and finally to investigate the possibility of forming 4, 6, 7 and 8 membered rings using a similar methodology.

3.2 Various substitution patterns

In the first two chapters we studied the substitution on the 1, 3 and 5 positions around the 4-nitropyrrolidinone rings *via* a nitro-Mannich / lactamisation cascade. We demonstrated that the reaction was extremely broad in scope and could tolerate a wide variety of functional groups. However, it could be argued that two crucial examples were missing; the ones where the 1 and 5 positions are substituted by hydrogen atoms; see for example 5-substituted-4-nitropyrrolidinones **198** and 1-substituted-4-nitropyrrolidinones **199** respectively (Figure 12). Also, we believed it would be interesting to attempt the cascade with a methyl 3-alkylsubstituted-3-nitropropanoate, as if successful 1,4,5-trisubstituted-4-nitropyrrolidinones **200** would be formed (Figure 12).

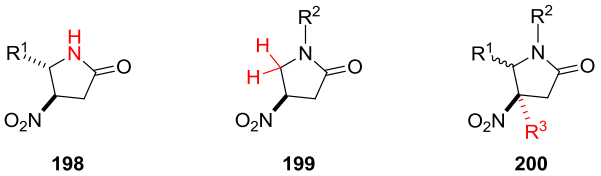
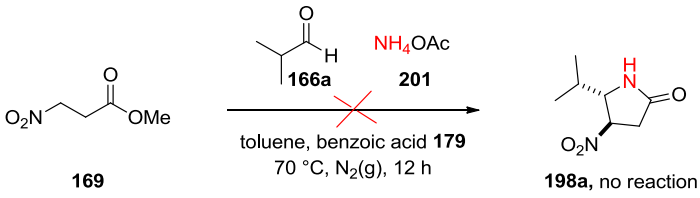


Figure 12 – New target molecules

3.2.1 First target: 5-substituted-4-nitropyrrolidinones 198

In order to synthesise 5-substituted-4-nitropyrrolidinones **198**, the nitro-Mannich / lactamisation cascade had to be performed with an equivalent of ammonia as the amine. Although it may look like trivial, it turned out to be a difficult transformation and a long battle to concede the desired product.

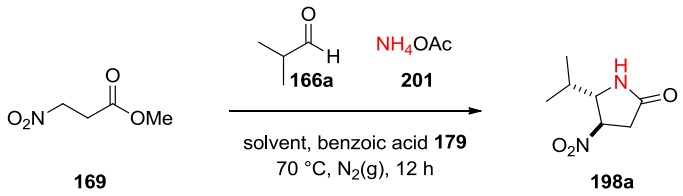
A first test reaction was done with ammonium acetate **201** (5.0 eq) and isobutyraldehyde **166a** (1.5 eq) under our optimised cascade conditions: nitroester **169** (1 eq), benzoic acid **179** (1.5 eq) and toluene (0.25 mol/L) (Scheme 71).



Scheme 71 – Attempted nitro-Mannich / lactamisation cascade with ammonium acetate

Unfortunately, under these conditions, none of the desired product **198a** was isolated. It appeared that changing primary amines **167** for an ammonium salt was modifying the reactivity of the system and a solvent screen was undertaken.

Several reactions were performed with nitroester **169**, isobutyraldehyde **166a**, ammonium acetate **201** and benzoic acid **179** at 65 °C in various solvents ranging from polar protic to apolar aprotic. The yields and the diastereomeric ratios were measured by ^{1}H NMR spectroscopy on the crude mixture and the results are presented in Table 21.



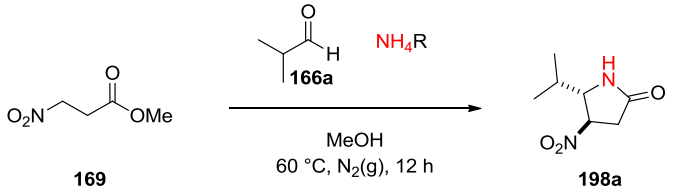
Entry	Solvent	^{1}H NMR yield of 198a (%)	dr
1	Water	-	-
2	MeOH	66%	> 98:2
3	EtOH	34%	> 98:2
4	CH_3CN	33%	> 98:2
5	THF	38%	> 98:2
6	DMF	Traces	-
7	DMSO	Traces	-
8	$CHCl_3$	26%	> 98:2
9	Toluene	-	-
10	Hexane	-	-

Table 21 – Solvent screen

Although no product was observed in apolar aprotic solvents such as toluene and hexane (entries 9 and 10), pleasingly with polar aprotic solvents such as tetrahydrofuran and acetonitrile (entries 4 and 5), the reactions were efficient and diastereoselective. Further screening revealed methanol to be optimal with respect to both reaction yield and diastereoselectivity (entry 2).

The reaction was repeated on 100 mg scale in methanol and the desired pyrrolidinone **198a** was isolated in 28% yield. Clearly the reaction required some further optimisation.

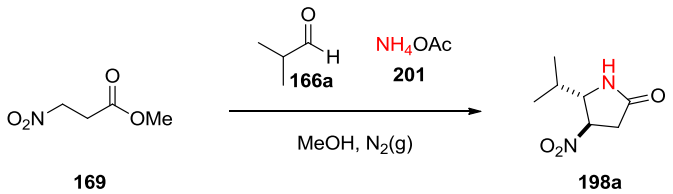
Six experiments were set up to test the influence of various parameters on the reaction. The results are presented in Table 22.



Entry	Ammonia (eq)	166a (eq)	Concentration (mol/L)	Benzoic acid 179	Conversion 198a (%)
1	NH_4OAc **201** (5.0 eq)	1.5 eq	0.25 mol/L	-	85%
2	NH_4HCO_2 **202** (5.0 eq)	1.5 eq	0.25 mol/L	-	57%
3	NH_4OAc **201** (5.0 eq)	5.0 eq	0.25 mol/L	-	99%
4	NH_4OAc **201** (5.0 eq)	1.5 eq	0.75 mol/L	-	92%
5	NH_4OAc **201** (5.0 eq)	1.5 eq	0.25 mol/L	1.5 eq	75%
6	NH_4OAc **201** (1.5 eq)	1.5 eq	0.25 mol/L	-	54%

Table 22 – various

Replacing ammonium acetate **201** (entry 1) for ammonium formate **202** (entry 2) resulted in a strong decrease of the conversion, measured by ^{1}H NMR spectroscopy, after 12 hours. The yield was also reduced by lowering the quantity of ammonium acetate **201** from 5.0 equivalents to 1.5 equivalents (entry 6) or adding 1.5 equivalents of benzoic acid **179** (entry 5). Pleasingly, increasing the stoichiometry of isobutyraldehyde **166a** from 1.5 equivalents to 5.0 equivalents or increasing the concentration of the reaction mixture enabled the formation of pyrrolidinone **198a** in 99% and 92% conversion respectively (entries 3 and 4). However, the isolated yields were always significantly lower than the conversion observed by ^{1}H NMR spectroscopy and the product was suspected to be affected by the reaction temperature. Accordingly, a temperature screen was undertaken and the isolated yields are presented in Table 23.

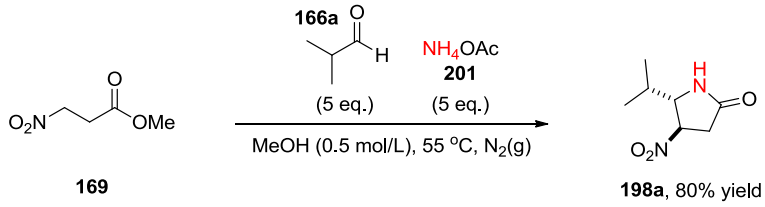


Entry	Temp. (˚C)	MeOH (mol/L)	Time	Isolated yield of 198a (%)
1	RT	0.25 mol/L	6 days	76%
2	35 ˚C	0.25 mol/L	6 days	55%
3	55 ˚C	0.25 mol/L	30 h	68%
4	70 ˚C	0.25 mol/L	8 h	40%
5	RT	-	6 days	35%

Table 23 – Temperature screen

As expected, the isolated yield increased with decreasing temperature and the desired product **1a** was isolated in 40% yield at 70 °C (entry 5) *versus* 76% yield at room temperature (entry 1). Nevertheless, at room temperature the reaction required a long reaction time of 6 days. A temperature of 55 °C was considered to provide an acceptable compromise between the efficiency of the reaction and the reaction time: 68% yield after 30 hours (entry 3).

Upon scale up and under our optimised conditions we were delighted to find that the reaction of nitroester **169** (1 eq) with isobutyraldehyde **166a** (5 eq) and ammonium acetate **201** (5 eq) in methanol (0.5 mol/L) at 55 °C provided pyrrolidinone **198a** in 80% yield after 24 hours (Scheme 72).



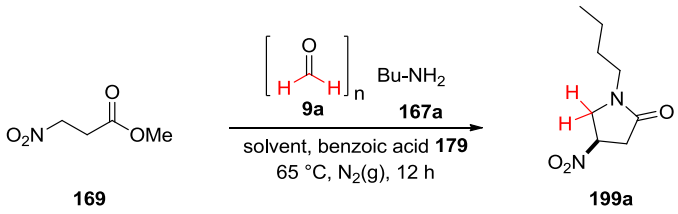
Scheme 72 – Optimum reaction conditions for the cascade with ammonium acetate

This was clearly a step forward and we were ready to move on to our next target: 1-substituted-4-nitropyrrolidinones **2**.

3.2.2 1-substituted-4-nitropyrrolidinones 199

With the aim of forming pyrrolidin-2-ones **199** bearing only hydrogen atoms in the 5 position, formaldehyde **9** had to be utilised as the aldehyde of the cascade reaction. Formaldehyde exists under two forms: as the polymer para-formaldehyde **9a** or as a 37% solution in water **9b**. In order to assess the reactivity of **9a** and **9b** to a nitro-Mannich / lactamisation cascade and to select the best reagent, two separate solvent screens were undertaken.

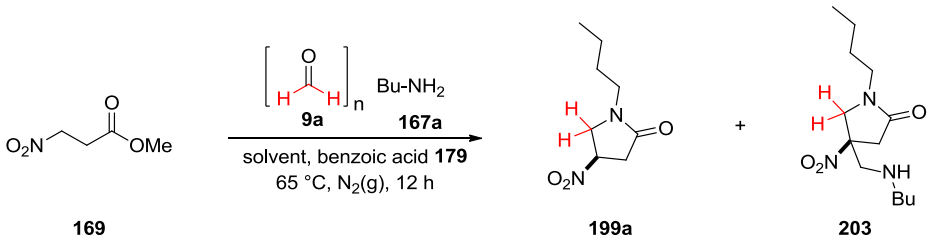
A first solvent screen was done to probe the reactivity of para-formaldehyde. The reaction of nitroester **169** (1 eq) with para-formaldehyde **9a** (1.5 eq), butylamine **167a** (1.5 eq) and benzoic aicd **179** (1.5 eq) was performed at 65 °C in a wide variety of solvents ranging from polar protic to apolar aprotic (Table 24).



Entry	Solvent	^{1}H NMR yield of 199a (%)
1	Water	-
2	MeOH	-
3	EtOH	-
4	CH_3CN	traces
5	THF	50%
6	DMF	-
7	DMSO	traces
8	$CHCl_3$	50%
9	Toluene	-
10	Hexane	-

Table 24 – Solvent screen with para-formaldehyde 9a

The crude reaction mixtures were analysed by ^{1}H NMR spectroscopy and pyrrolidinone **199a** was observed only in two reactions: with acetonitrile and chloroform, and in both cases the conversion had reached 50% after 12 hours (entries 5 and 8). Those two reactions were repeated and the conversion monitored by TLC. After 24 hours, both reactions had reached full conversion and the crude products were purified by flash column chromatography (Table 25).



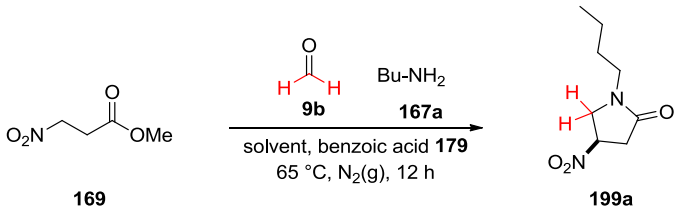
Entry	Solvent	Isolated yield (%)	199a/203
1	THF	63%	**203** only
2	$CHCl_3$	99%	1:1

Table 25 – Reaction in tetrahydrofuran and chloroform

From reaction in tetrahydrofuran, only one product was isolated in 63% yield which, after full data analysis, was determined to be compound **203**, the product of a double nitro-Mannich reaction and a lactamisation (entry 1). The reaction in chloroform (entry 2) provided a 1:1 mixture of desired product **199a** and side product **203** in 99% yield.

A second solvent screen was done to probe the reactivity of the 37% solution of formaldehyde **9b** in water. The reaction of nitroester **169** (1 eq) with formaldehyde **bb** (1.5 eq), butylamine **167a** and

benzoic acid **179** was performed at 65 °C in a wide variety of solvents ranging from polar protic to apolar aprotic. The conversion was measured by ^{1}H NMR spectroscopy and the results are presented in Table 26.

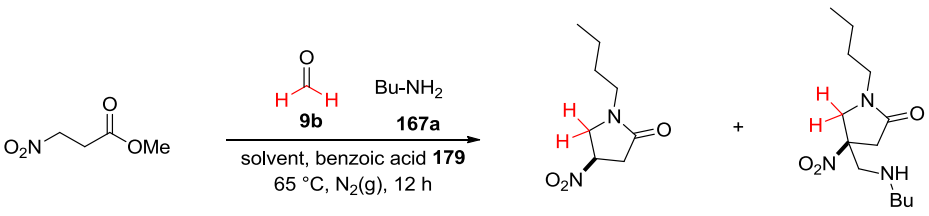


169 **199a**

Entry	Solvent	Conversion of 199a (%)
1	Water	-
2	MeOH	-
3	EtOH	-
4	CH_3CN	62%
5	THF	31%
6	$CHCl_3$	-
7	Toluene	90%
8	Hexane	-

Table 26 – Solvent screen with formaldehyde 9b (37% in water)

The crude reaction mixtures were analysed by ^{1}H NMR spectroscopy and pyrrolidinone **199a** was observed in three reactions: with acetonitrile, tetrahydrofuran and toluene, in 62%, 31% and 90% conversions respectively after 12 hours (entries 4, 5 and 7). The two best reactions were repeated and the conversion monitored by TLC. After 24 hours, both reactions had reached full conversion and the crude products were purified by flash column chromatography (Table 27).



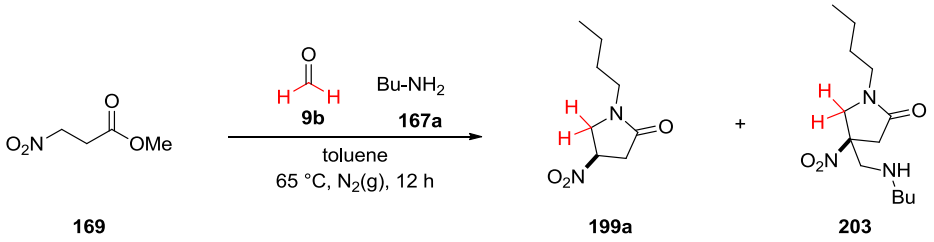
169 **199a** **203**

Entry	Solvent	Isolated yield (%)	199a/203
1	CH_3CN	10%	> 30:1
2	Toluene	33%	> 30:1

Table 27 – Reaction in acetonitrile and toluene

Pleasingly, in acetonitrile and toluene only the desired pyrrolidinone **199a** was formed in 10% and 33% yields respectively and the side product **203** was not observed (entries 1 and 2). Accordingly, reaction in toluene with formaldehyde **9b** (37% in water) was selected for the rest of the optimisation studies.

Further experiments were undertaken to probe the effect of the stoichiometry and the presence of benzoic acid **179** on the reaction. The results are presented in Table 28.

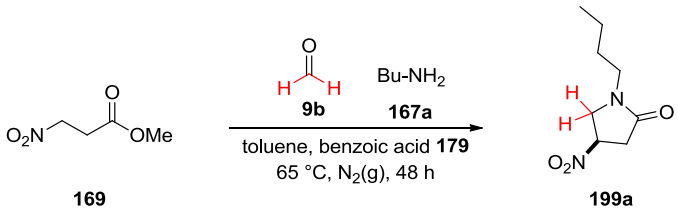


169 **199a** **203**

Entry	Butylamine (eq)	9b (eq)	Concentration (mol/L)	Benzoic acid 179	yield (%)
1	1.5 eq	1.5 eq	0.25 mol/L	-	bis
2	1.5 eq	1.5 eq	0.25 mol/L	1.5 eq	33%
3	5.0 eq	5.0 eq	0.25 mol/L	-	Bis
4	0.8 eq	0.8 eq	0.25 mol/L	-	Bis

Table 28 – Optimisation of the stoichiometry of the reagents

Interestingly, the presence of benzoic acid **179** proved to be crucial for the formation of desired product **199a** and another screen was performed in the presence of 1.5 equivalents of benzoic acid **179** (Table 29).



169 **199a**

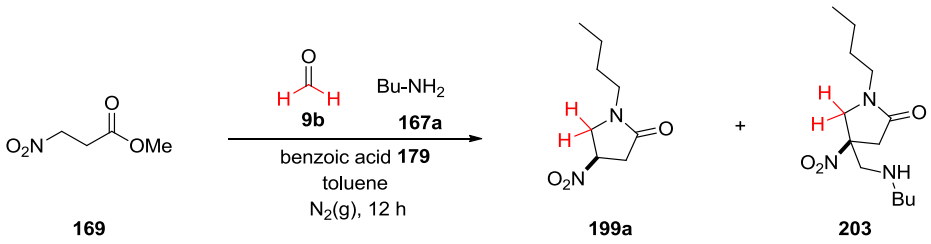
Entry	Butylamine (eq)	9b (eq)	Concentration (mol/L)	Yield 199a (%)
1	1.5 eq	1.5 eq	0.25 mol/L	48%
2	1.0 eq	1.0 eq	0.25 mol/L	37%
3	0.8 eq	0.8 eq	0.25 mol/L	31%
4	1.5 eq	1.5 eq	0.12 mol/L	60%
5	1.5 eq	1.5 eq	0.75 mol/L	30%

Table 29 – Optimisation of the stoichiometry and the concentration

The overall progression of the reaction was found to decrease with decreasing equivalents of formaldehyde **9b** and amine **167a** from 48% with 1.5 equivalents of the imine to 31% conversion with 0.8 equivalents (entries 1-3). However, the reaction proved to perform better at higher dilutions (entry 4) than at lower ones (entry 5).

Another screen was undertaken to investigate further the influence of the dilution and the temperature on the reaction efficiency and selectivity. The reaction of nitroester **169** (1 eq) with

formaldehyde **9b** (1.5 eq), butylamine **167a** and benzoic acid **179** (1.5 eq) was performed in toluene with different concentrations and temperature. The results are presented in Table 30.

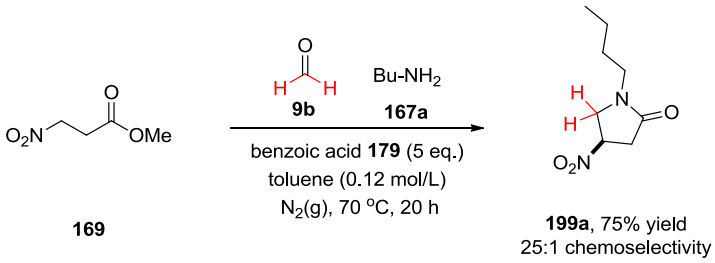


Entry	Temp. (˚C)	Concentration (mol/L)	^{1}H NMR yield	199a/203
1	55 ˚C	0.25 mol/L	24%	2.0:1
2	55 ˚C	0.12 mol/L	61%	1.2:1
3	55 ˚C	0.06 mol/L	63%	1.0: 3
4	70 ˚C	0.12 mol/L	85%	25.0:1

Table 30 – Optimisation of the temperature

It was confirmed that higher dilution increased the overall reaction yield; however, it also favoured the formation of side product **203**. Indeed, at a concentration of 0.25 mol/L, **199a** was the major product formed in a 2:1 ratio (entry 1), at 0.12 mol/L, both product were formed in quasi equimolar quantities (entry 2) and at 0.06 mol/L, products were formed in a 1:3 ratio in favour of the side product **203**. Interestingly, increasing the temperature from 55 °C to 70 °C resulted in a strong selectivity bias for the desired product **199a**, which was isolated in a 25:1 ratio at 0.12 mol/L (entry 4). By assuming that the nitro-Mannich reaction is reversible, at high temperatures the side product **203** is probably entropically unfavoured and mainly the desired product **199a** is formed.

Pleasingly, under our optimised conditions and upon scale up, the reaction of nitroester **169** with formaldehyde **9b** (1.5 eq) and butylamine **167a** (1.5 eq) in toluene (0.12 mol/L) at 70 °C, with a large excess of benzoic acid (5 eq) performed smoothly and **2a** was isolated as the major compound in the reaction (25:1 selectivity) in a very good yield (75%) (Scheme 73).

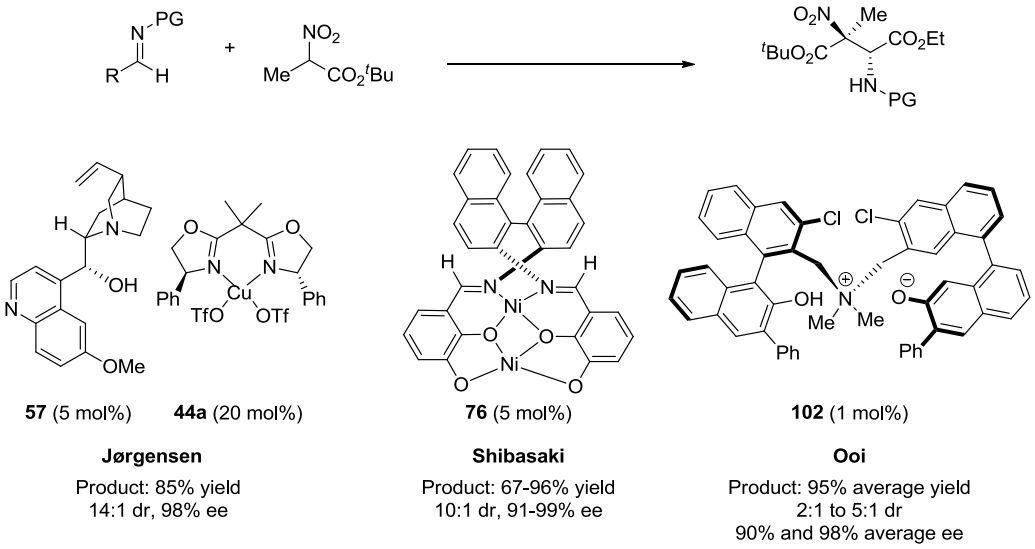


Scheme 73 –Optimum reaction conditions for the cascade with formaldehyde 7b (37% solution in water)

We had now successfully synthesised 2 of our 3 targets and there was one further substitution pattern we wanted to investigate, the 4-nitropyrrolidinone **200** substituted in the 4 position.

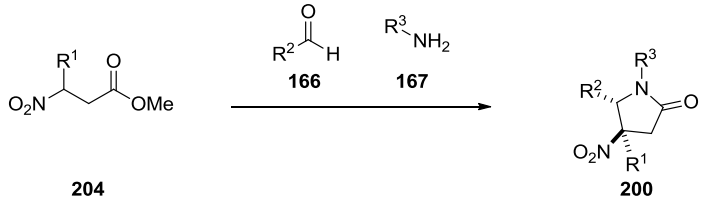
3.2.3 1,4,5-Trisubstituted-4-nitropyrrolidinones

The products of a nitro-Mannich reaction bearing a quaternary centre alpha to the nitro group, has been reported in the literature. Indeed, in the introduction, we described the nitro-Mannich reaction of *N*-protected imine with ^{t}butyl-2-nitropropionate **56** to form α-nitro-β-amino esters discovered by Jørgensen,[75] Shibasaki[76] and Ooi[77] independently (Scheme 74).



Scheme 74 – Formation of quaternary centers alpha to the nitro group *via* Nitro-Mannich reaction

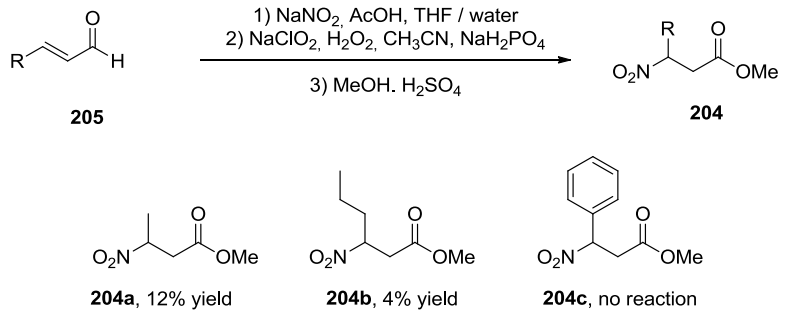
Accordingly, we believed that if we could synthesise substituted nitroester **204**, their subsequent reaction with an aldehyde **166** and an amine **167** *via* a nitro-Mannich / lactamisation cascade could, in theory, lead to the desired pyrrolidinones **200** (Scheme 75).



Scheme 75 – Proposed nitro-Mannich / lactamisation cascade with methyl 3-alkyl-3-nitropropanoate 204

[75] Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.
[76] Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.
[77] Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878.

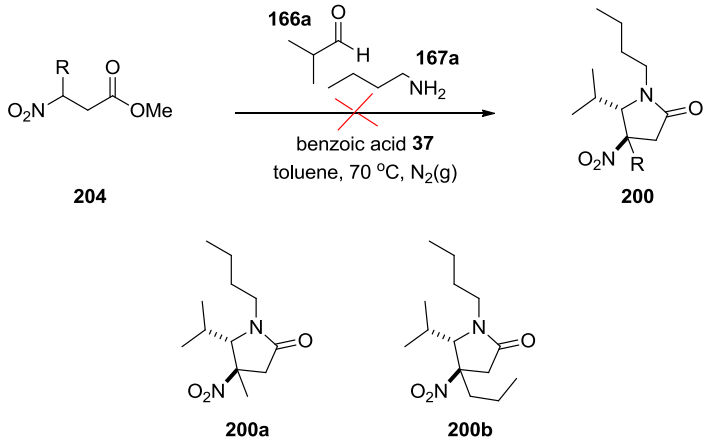
This approach required, prior to the reaction cascade, the synthesis of 3-alkyl-3-nitropropanoate **204**. This was achieved in a similar fashion as for the synthesis of methyl 3-nitropropanoate **169**, in three steps from the α,β-unsaturated aldehyde precursor **205**. Crotonaldehyde **205a**, trans-2-hexen-1-al **205b** and cinnamaldehyde **205c**, three commercially available α,β-unsaturated aldehyde, were used as starting materials. The nucleophilic addition of nitrite to aldehydes **205**, followed by a Pinnick oxidation and finally an esterification reaction allowed the formation of methyl 3-methyl-3-nitropropanoate **204a** in 12% overall yield and methyl 3-nitro-3-^{n}propylpropanoate **204b** in 4% overall yield (Scheme 76). Unfortunately, none of the methyl 3-nitro-3-phenylpropanoate **204c** was isolated, as the more conjugated starting material is probably less reactive.



Scheme 76 – Synthesis of methyl 3-alkyl-3-nitropropanoate 204a and 204b

The overall yields of the reactions were low, but the desired product **204a** and **204b** had been isolated in sufficient quantities to attempt the nitro-Mannich / lactamisation cascade.

The attempted cascade reactions of nitroesters **204a** and **204b** were performed with isobutyraldehyde **166a** (1.5 equivalents), butylamine **167b** (1.5 equivalents) and benzoic acid **179** (1.5 equivalents) in toluene at 70 °C (Scheme 77).



Scheme 77 – Attempts at a nitro-Mannich / lactamisation cascade with methyl 3-alkyl-3-nitropropanoate 204

Both reactions were allowed to stir for seven days, but no reaction could be observed and only the starting materials were recovered after purification by flash column chromatography. We believe that the lack of reactivity of this system is due to steric hindrance and this will be detailed in chapter 5 which describes our mechanistic investigation.

3.3 Synthetic utility of the nitro-Mannich product

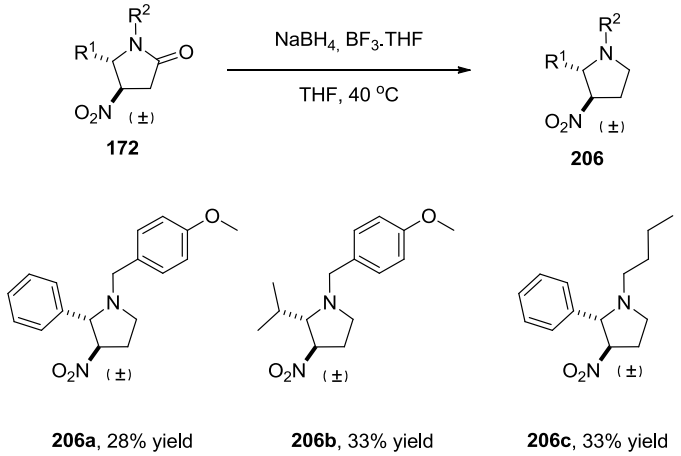
In chapters 1 and 2 and the beginning of this chapter, different methods were developed to enable the efficient and easy synthesis of 4-nitropyrrolidinones with a wide variety of substitution patterns in the 1, 3 and 5 positions. Pyrrolidin-2-ones, as such, are interesting motifs which are recurrent in both natural product and biologically active compounds. In addition, the presence of a nitro group and a carbonyl group allows the possibility of further functional group modifications leading to an even broader range of compounds; the nitro group can be reduced to the corresponding amine or be removed *via* a radical reaction and the lactam carbonyl can be reduced to the amine.

First, a series of functional group modifications around the nitro-pyrrolidin-2-one ring will be performed to emphasise the importance of our method in the context of a total synthesis or of a library synthesis. Then, studies towards the total synthesis of crispin A **130** will be reported.

3.3.1 Functional group modification around the ring

The reductions of a nitro group and of a lactam carbonyl have been reported independently. However it would be interesting to see if we can reduce them selectively, sequentially and simultaneously.

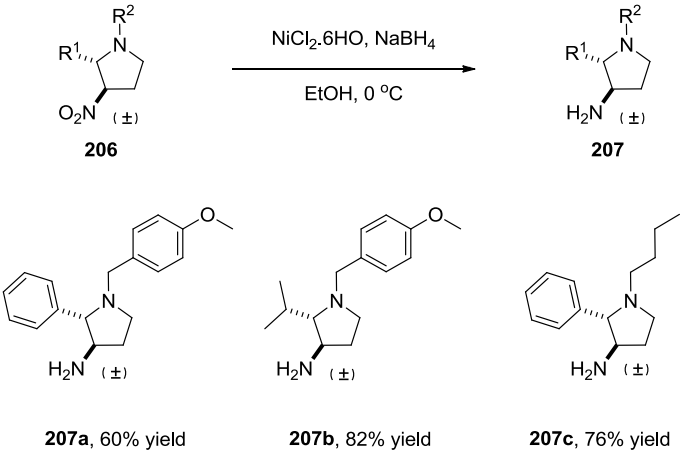
The reduction of lactam carbonyl group by sodium borohydride and boron trifluoride in THF at 40 °C has been reported. However, we did not know if these conditions would be inert to the nitro group and, accordingly, tests reactions were undertaken on three 1,5-disubstituted nitro-pyrrolidinones **172rv**, **172av** and **172ra** bearing different substituent in the 1 and 5 positions (Scheme 78).



Scheme 78 – Selective reduction of the carbonyl of lactams 172

Pleasingly, the carbonyl group was indeed successfully reduced in the presence of the nitro group and 1,2-disubstituted-3-nitropyrrolidines **206a**, **206b** and **206c** were isolated by flash column chromatography in unoptimised 28%, 33% and 33% yield respectively. The products were fully characterised and the presence of the nitro group was unambiguously confirmed by ^{13}C NMR spectroscopy and infrared spectroscopy.

Further reductions of the previously synthesised 3-nitropyrrolidines **206** with nickel boride, formed from the reaction of nickel chloride hexahydrate and sodium borohydride in ethanol at 0 °C were attempted (Scheme 79).

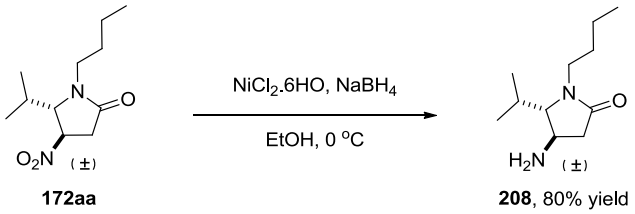


Scheme 79 – Reduction of the nitro group to the corresponding amines 207

We were delighted to find that the nitro group of 3-nitropyrrolidines **206a**-**c** were reduced efficiently to the corresponding pyrrolidine amines **207a**-**c** in 60%, 82% and 76% unoptimised yields

respectively. Interestingly, the simultaneous reduction of the nitro group and the lactam carbonyl of **172** with lithium aluminium hydride failed to form any of the corresponding products **207**.

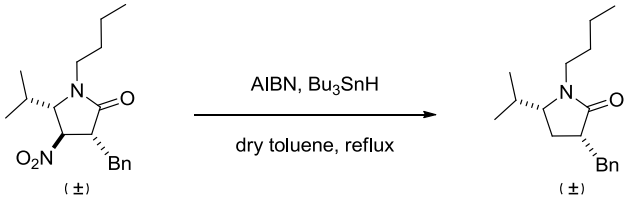
However, the nickel boride reaction conditions allowed the selective reduction of the nitro group of pyrrolidinone **172aa** selectively in the presence of the lactam carbonyl in 80% yield to form **208** (Scheme 80).



172aa **208**, 80% yield

Scheme 80 – Selective reduction of the nitro group in the presence of the lactam carbonyl

We had successfully reduced the nitro group and the lactam carbonyl selectively and sequentially. We then attempted the reductive removal of the nitro group with AIBN and Bu_3SnH in refluxing toluene, using a modification of the Ono protocol,[78] on pyrrolidinone **193aaa** (Scheme 81).



193aaa **209**, 90% yield

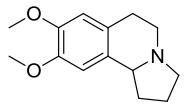
Scheme 81 – Reductive removal of the nitro group

Pleasingly, this was successfully and 3-benzyl-1-butyl-5-isopropylpyrrolidin-2-one **209** was isolated in an excellent yield (90%).

3.3.2 Attempted application to the synthesis of natural product Crispin A

In 2002, a new indolizidine alkaloid known as crispin A[79] **130** (Figure 13) was isolated from *Carduus crispus*, a popular invasive plant occurring in Asia and Europe, which was found to exhibit good antitumor activity against SKOV3, KB and HeLa human cancer lines.

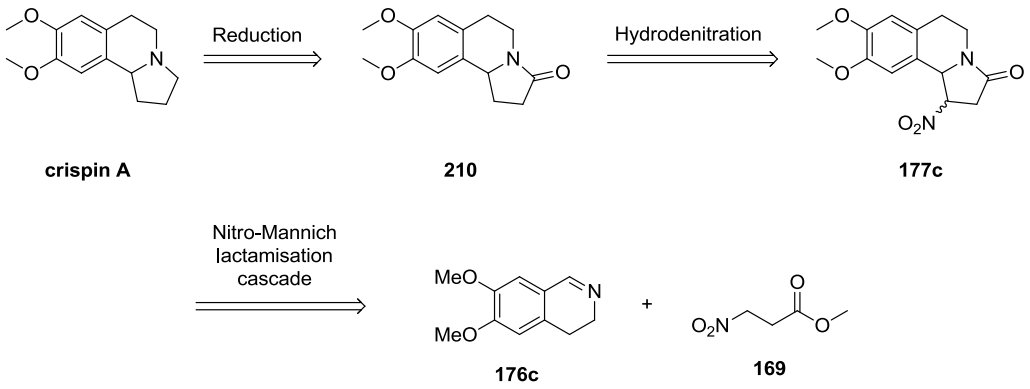
[78] Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1750.
[79] Isolation: Zhang, Q.; Tu, G.; Zha, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795.



130

Figure 13 – Crispin A

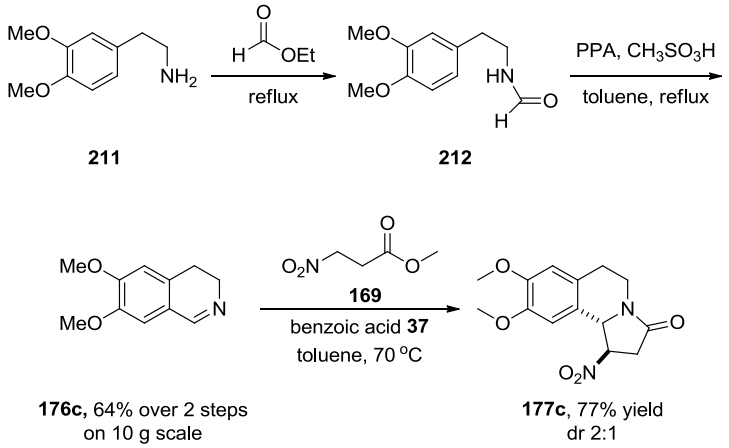
The fused tricyclic pyrrolidine structure of crispin A **130** made it a perfect target to demonstrate the utility of the previously developed nitro-Mannich / lactamisation cascade with preformed cyclic imines. This would represent a nice addition to our work. In theory, crispin A **130** could be formed in three steps from methyl nitropropanoate **169** and cyclic imine **176c**. First a nitro-Mannich / lactamisation cascade would enable the construction of the fused tricyclic core structure of **177c**, then reductive removal of the nitro group and subsequent reduction of the lactam carbonyl would give rise to crispin A **130** (Scheme 82).



Scheme 82 – A three step retrosynthesis of crispin A

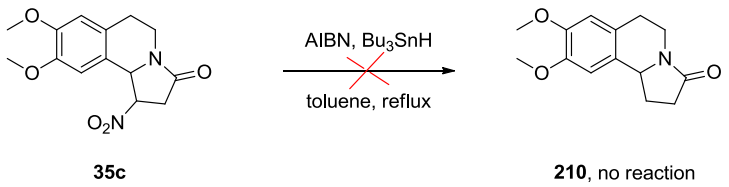
6,7-Dimethoxy-3,4-dihydroisoquinoline **176c**[80] was synthesised in 2 steps from dimethoxyphenylethylamine **211** *via* a Bischler-Napieralski reaction. Then, a nitro-Mannich / lactamisation cascade with methyl 3-nitropropanoate **169** was achieved in 77% yield and the desired pyrrolidinone **177c** was formed with a diastereomeric ratio of 2:1 (Scheme 83).

[80] Warrener, R. N. *Tetrahedron* **1998**, *54*, 7485.



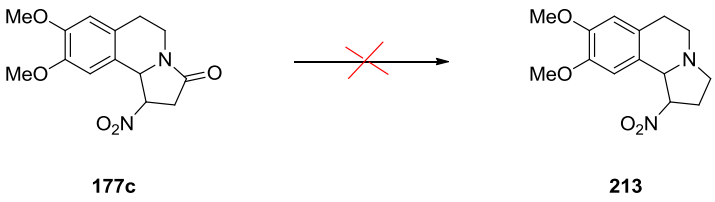
Scheme 83 – Synthesis of fused tricyclic pyrrolidinone 177c.

The reductive removal of the nitro group of nitropyrrolidinone **177c** with AIBN and Bu_3SnH was attempted several times but unfortunately, pyrrolidinone **210** was never formed (Scheme 84).



Scheme 84 – Failed attempts at a reductive removal of the nitro group

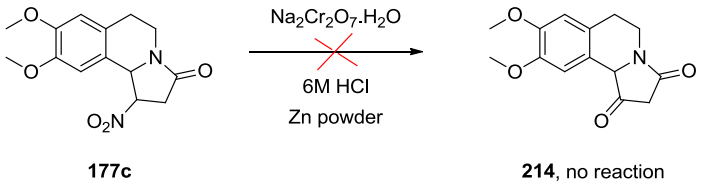
The reason for this lack of reactivity was unclear but instead of investigating it further it was decided to first reduce the lactam carbonyl and then to attempt the reductive removal of the nitro group afterwards. Several conditions to reduce the carbonyl group of pyrrolidinone **177c** were attempted and the results are presented in Table 31.



Entry	Conditions	Yield of 213 (%)
1	Hantzsch ester, Tf_2O, CH_2Cl_2	-
2	$NaBH_4$, BF_3.THF, THF	-
3	$NaBH_4$, I_2, THF	-
4	BH_3, THF	-
5	$RhH(CO)(PPh_3)_3$, Ph_2SiH_2, THF	-
6	$RhCl(PPh_3)_3$, Ph_2SiH_2, THF	-

Table 31 – Failed attempts at reducing the lactam carbonyl

Strangely none of the reagent systems trialled provided any of the desired pyrrolidine **213** and therefore a less direct approach was attempted. The reaction of nitro-pyrrolidinone **177c** under classic Nef conditions was hoped to provide pyrrolidinone **214** bearing two carbonyl moieties (Scheme 85). If this was successful we could envisage a sequential reduction of the ketone (*via* a Wolf kishner reaction for example) and then of the lactam carbonyl. A number of typical conditions were tried and one is presented in Scheme 85.

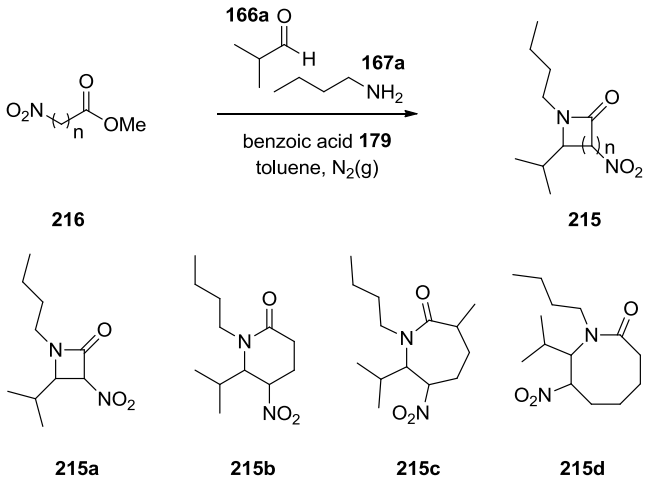


Scheme 85 – Failed attempt at a Nef reaction

Unfortunately, all the conditions tried for the Nef reaction failed to form the desired product **214**. Clearly, fused tricyclic pyrrolidinone **177c** had some weird and unexplained lack of reactivity. Completing the total synthesis of crispin A would have been a very nice addition to our work on nitro-Mannich / lactamisation cascades; however considering the simplicity of the target, we decided, for cost effective reason to stop our effort towards the synthesis of crispin A **130**.

3.4 Attempts at extending the method to 4, 6, 7 and 8 membered rings

Finally, the optimised reaction conditions developed for the synthesis of nitropyrrolidinones *via* a nitro-Mannich lactamisation cascade were attempted on various nitroesters with different carbon chain length to form the corresponding 3-nitrocyclobutan-2-one **215a**, 5-nitropiperidin-2-one **215b**, 6-nitrocyclohepten-2-one **215c** and 7-nitrocyclocten-2-one **215d** (Scheme 86).

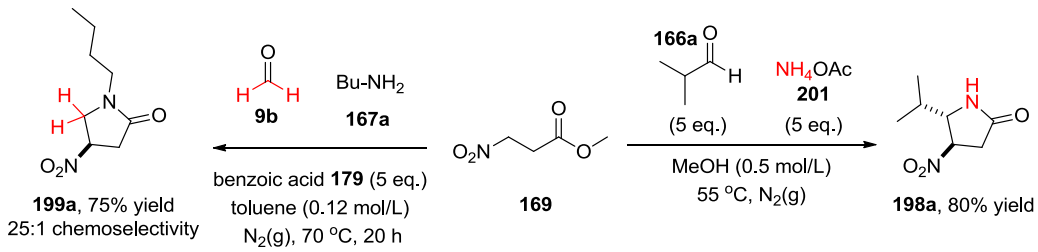


Scheme 86 – Failed attempts at the synthesis of 4, 6, 7 and 8 membered ring pyrrolidinones 215

In all cases the reaction failed to provide any of the desired products **215a**, **215b**, **215c** and **215d**. A wide solvent screen was undertaken to try and synthesise **215a** but it was never formed. At this point, other projects became a priority and we never came back to it. However, we believe that it would be some interesting work for the future, and especially the synthesis of 7-membered ring **215c**.

3.5 Conclusion

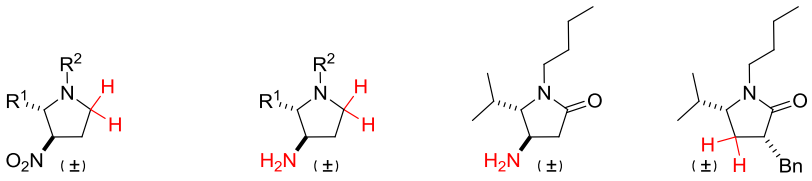
In this chapter, the nitro-Mannich / lactamisation cascade of **169** was developed further to allow the rapid synthesis of 5-isopropyl-4-nitropyrrolidin-2-one **198a** from reaction with ammonium acetate **201** and 1-butyl-4-nitropyrrolidin-2-one **199a** from reaction with formaldehyde **9b** (37% solution in water) (Scheme 87).



Scheme 87 – Further extension of the nitro-Mannich / lactamisation cascade

In addition, the synthetic utility of the nitro-pyrrolidinones formed was exemplified through various functional group modifications. The selective reduction of the lactam carbonyl was performed in the

presence of the nitro group, the reduction of the nitro group to the corresponding amine was achieved successfully in the presence or absence of carbonyl group and the nitro group was successfully removed under radical conditions. (Scheme 88).



206, 31% average yield **207**, 73% average yield **208**, 80% yield **209**, 90% yield

Scheme 88 – Various functional group modifications

CHAPTER 4

Studies Towards

an

Enantioselective Nitro-Mannich / Lactamisation Cascade

4.1 Context

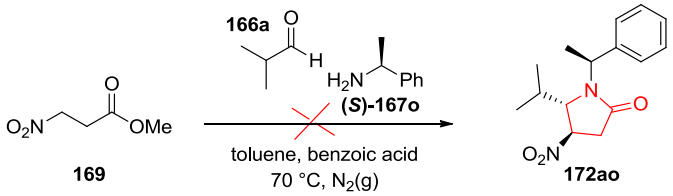
In chapter 1, we described the first nitro-Mannich / lactamisation cascade for the synthesis of *trans* 1,5-disubstituted 4-nitropyrrolidin-2-ones, and in the following chapters, this work was extended to the synthesis of pyrrolidinones with various substitution patterns: 1,3,5-trisubstituted 4 nitropyrrolidin-2-ones (chapter 2), 5-substituted 4-nitropyrrolidin-2-ones and 1-substituted 4-nitropyrrolidin-2-ones (chapter 3). In order to advance this work further, we decided to investigate an enantioselective version of our nitro-Mannich / lactamisation cascade for the synthesis of enantiomerically enriched (enantioenriched) pyrrolidin-2-ones.

As seen in the introduction, various methods have been developed over the past 30 years to perform enantioselective nitro-Mannich reactions. These methods involved either the use of organometallic catalysts or organocatalysts and the products can be obtained with excellent degrees of both diastereo- and enantiocontrol. However, the scope of the reaction with respect to the imine is, in many cases, very limited. Nevertheless, there are no examples in the literature of an enantioselective nitro-Mannich / lactamisation cascade and, in this chapter, we describe the details of our studies on this subject.

4.2 First approaches

4.2.1 Use of enantiopure chiral amines

The first reaction attempted, to form an enantioenriched pyrrolidin-2-one, employed enantiopure (*S*)-1-phenylethanamine **167o** in order to induce stereocontrol in the reaction cascade towards **172ao** (Scheme 89).



Scheme 89 – Use of an enantiopure chiral amine in the nitro-Mannich / lactamisation cascade

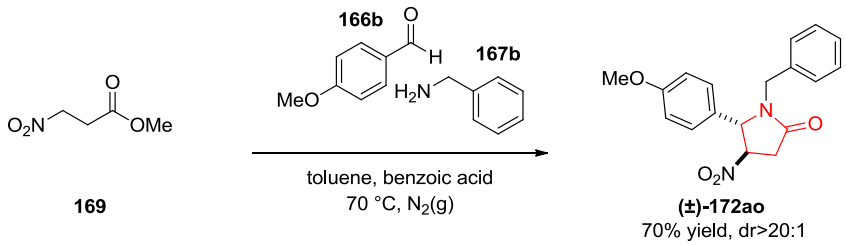
Unfortunately, the reaction of methyl 3-nitropropanoate **169** with isobutyraldehyde **166a** and (*S*)-1-phenylethanamine **167o** under our optimised conditions failed to provide any of the desired product **172ao**, even after it was allowed to stir for several days. We believe that the reaction failed due to the steric hindrance of the amine (see chapter 1 and chapter 5).

Although disappointing, our primary objective was to develop an enantioselective reaction with an achiral nitroester, an aldehyde and an amine, and to induce chirality with a chiral catalyst.

4.2.2 Broad catalyst screen on a model system

In order to develop an enantioselective version of our nitro-Mannich / lactamisation cascade for the synthesis of pyrrolidinones, we decided to select a model system, bearing UV active moieties (chosen to assist analysis of the product by HPLC), and to perform the reaction in the absence of benzoic acid but with various catalysts. Accordingly, nitroester **169**, benzylamine **167b** and *p*-anisaldehyde **166b** became our reagent system of reference for this study.

First, pyrrolidinone **172ao** was synthesised in 70% yield as a racemic mixture, using our previously optimised conditions (Scheme 90).



Scheme 90 – Synthesis of (±)-172ao

With the racemic product **172ao** in hand and the proper conditions for the separation of the two enantiomer by lHPLC using chiral supported columns, we were ready to start the catalyst screen.

Two chiral phosphoric acids, (*R*)-**216** and (*R*)-**217**, two bifunctional catalysts urea **218** and thio-urea **159** (derived from cinchonine), bisoxazoline ligand **219** (in combination with metal species) and BINAP ligands **220** (in combination with metal species) were selected (Figure 14).

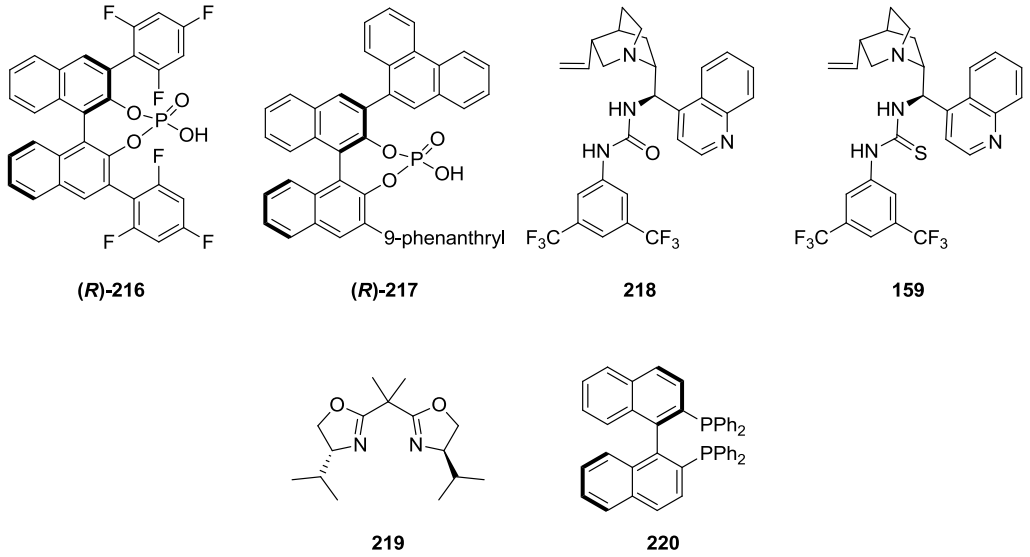
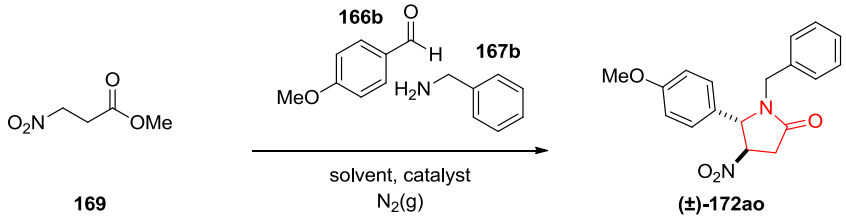


Figure 14 – Catalysts

We first probed the reactivity of the model system with catalysts (*R*)-**216**, (*R*)-**217**, **218** and **159**, used in catalytic amounts (10 mol%), in toluene at 70 °C (Table 32, entries 1-7). We then investigated the use of bisoxazoline ligands (BOX ligands) with various metals. BOX ligands are chiral organic compounds which, in combination with a metal ion, form organometallic complexes that can be used as chiral catalysts for a range of reactions. Box ligand **219**, bearing an isopropyl substituent, was used in combination with Pd(II), Cu(II) and Cu(I) in our model system in catalytic quantities (20 mol%) at 70 ^{o}C and at room temperature (Table 32, entries 8-15). Finally, BINAP ligands **220** associated with metals to form different organometallic complexes were then trialled (Table 32, entries 16-19).



Entry	Catalyst	Catalyst loading	Solvent	Temp. (°C)	Time (days)	172ao (%)	ee (%)
1	(*R*)-**216**	10%	Toluene	70 °C	1 day	42%	0%
2	(*R*)-**217**	10%	Toluene	70 °C	1 day	71%	0%
3	**218**	10%	Toluene	70 °C	1 day	47%	0%
4	**159**	10%	Toluene	70 °C	1 day	39%	5%
5	**159**	10%	THF	70 °C	1 day	20%	8%
6	**159**	10%	$CHCl_3$	70 °C	1 day	13%	10%
7	**159**	10%	Hexane	70 °C	1 day	10%	0%
8	**219**+$Pd(OAc)_2$	20%	Toluene	70 °C	2 days	44%	0%
9	**219**+$Cu(SO_3CF_3)_2$	20%	Toluene	70 °C	2 days	41%	0%
10	**219**+Cu(OTf)	20%	Toluene	70 °C	2 days	8%.	0%
11	**219**	20%	Toluene	70 °C	2 days	20%	0%
12	**219**+$Pd(OAc)_2$	20%	Toluene	RT	5 days	54%	0%
13	**219**+$Cu(SO_3CF_3)_2$	20%	Toluene	RT	5 days	46%	0%
14	**219**+ Cu(OTf)	20%	Toluene	RT	5 days	21%	0%
15	**219**+	20%	Toluene	RT	5 days	25%	0%
16	**220**+$Pd(OAc)_2$	20%	Toluene	70 °C	2 days	79%	-
17	**220**+$Cu(OTf)_2$	20%	Toluene	70 °C	2 days	-	-
18	**220**+Au(OTf)	20%	Toluene	70 °C	2 days	-	-
19	**220**+	20%	Toluene	70 °C	2 days	-	-

Table 32 – Catalyst and conditions screen

In most cases, the desired pyrrolidinone **172ao** was isolated in low to good yields ranging from 8% (entry 10) to 79% (entry 16). Only three reactions did not form any of the desired product **172ao** (entries 17-19). However, **172ao** was obtained as a racemic mixture in almost all reactions with the exceptions of catalyst **159** (entries 4-6) were a poor enantiomeric excess (5-10%) was measured.

At the light of those results, the reason for the absence of enantiomeric excess in the final product **172ao**, appeared to lie in the fact that the background (non-catalysed) reaction was faster than the catalysed reaction. Therefore, tweaking the reactivity of the system appeared to be a good solution to reduce the background reaction and therefore increase the degree of enantiocontrol.

4.2.3 Use of various *N*-protected imines

Most of the methodologies in the literature for an enantioselective nitro-Mannich reaction described the use of a *N*-protected imine. Among those, the most common protecting groups include *p*-Ts, Boc,

PMP (*p*-methoxyphenyl), OMP (*o*-methoxyphenyl) and PMB (*p*-methoxybenzyl) as well as, *N*-diphenyl-phosphinoyl imine. Accordingly, *N*-Tosyl-protected imine **221** and *N*-Boc-protected imine **222**, *N*-PMP-protected imine **223** and *N*-OMP-protected imine **224** were synthesised (Figure 15).

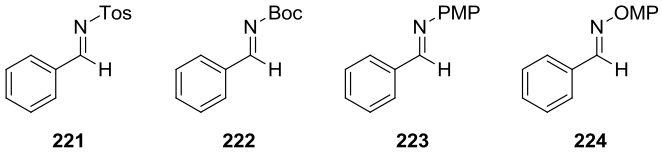
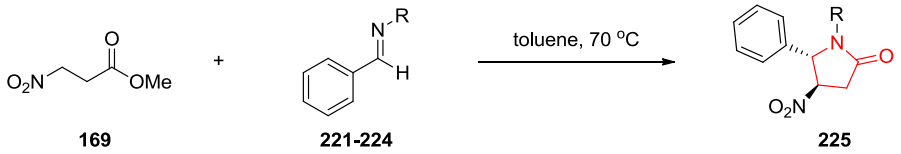


Figure 15– *N*-protected imines 221-224

They were then reacted with nitroester **169** to probe their reactivity in the nitro-Mannich / lactamisation cascade. Each imine was reacted under the corresponding reaction conditions: first without acid (to evaluate the occurance of uncatalysed reaction), and in the absence of uncatalysed reaction, with benzoic acid **179** and various catalysts (Table 33).



R= Tos, Boc, PMP, OMP

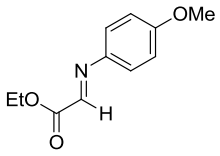
Entry	Imine	Acid	Time (days)	Conversion (%)
1	7	-	2 days	No reaction (NR)
2	7	benzoic acid **179**	2 days	NR
3	7	(*R*)-**180**	2 days	NR
4	8	-	2 days	NR
5	8	benzoic acid	2 days	NR
6	8	(*R*)-**180**	2 days	NR
7	9	-	5 days	26%
8	9	benzoic acid **179**	5 days	32%
9	10	-	2 days	NR
10	10	benzoic acid **179**	2 days	52%
11	10	(*R*)-**180**	2 days	NR
12	10	BOX **219** + $Cu(OTf)_2$	2 days	NR
13	10	BINAP **220** + $Cu(OTf)_2$	2 days	NR
14	10	**159**	2 days	NR

Table 33 – Reaction with *N*-protected-imines 221-224

According to the results displayed in Table 33, imines **221**, **222** and **224** were suitable for an enantioselective reaction as they did not react in the absence of catalysts (entries 1, 4 and 9). Unfortunately, no product was isolated either in the presence of acid, BOX or BINAP catalysts. The desired product **225** was isolated when nitroester **169** was reacted with *N*-PMP-protected imine **223**

in the absence of catalyst. Therefore imine **223** was deselected as a model imine for an enantioselective reaction *via* a catalytic process.

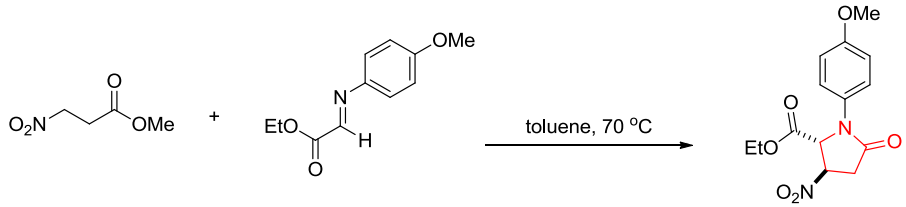
Imine **43** (Figure 16), synthesised from the condensation of *p*-anisidine with ethyl glyoxalate, is one of the widest used imines for enantioselective nitro-Mannich reactions.



43

Figure 16 – *N*-PMP-protected imine 43

A background reaction was performed with imine **43** and nitroester **169** in toluene at 70 °C, to verify that no reaction would proceed in the absence of catalyst (Scheme 91).



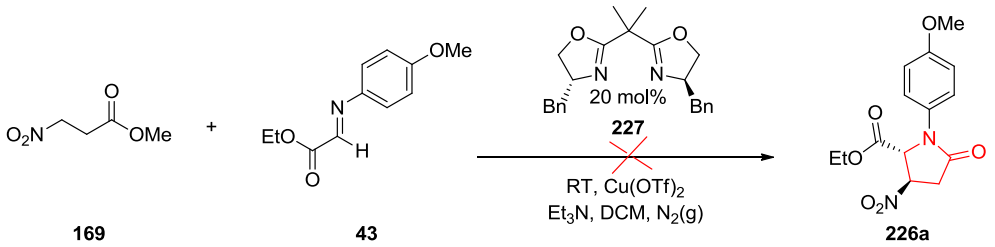
169 **43** **(±)-226a**

Scheme 91 – Checking the absence of background reaction between nitroester 169 and imine 43

Pleasingly, in absence of catalyst, none of the product **226a** was formed. This system of reagents seemed to be particularly interesting to start the development of a catalytic enantioselective reaction.

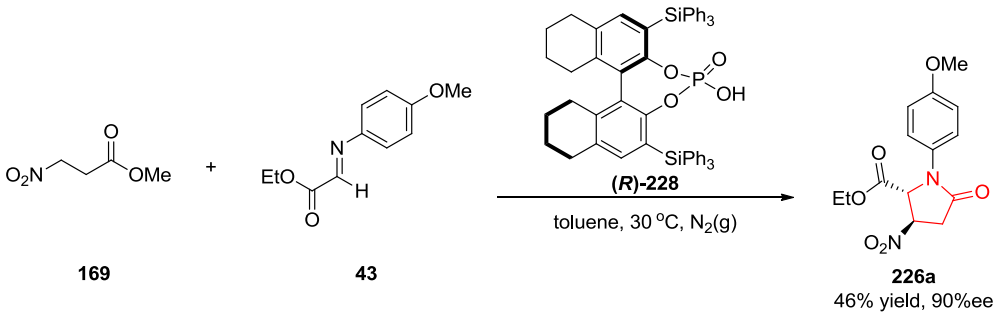
Two research groups, Jørgensen's group[81] and Rueping's group[82], described independently a different enantioselective nitro-Mannich reactions using imine **43**. Accordingly, two test reactions, on 15 mg scale of imine **43** and a large excess of nitroester **169** (10 equivalents), were set up with the best catalysts found in the literature procedures; one reaction used a Bn-BOX ligand **227** with Cu(II) in dichloromethane (Scheme 92) and the other, a chiral phosphoric acid (*R*)-**228** in toluene (Scheme 93).

[81] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.
[82] Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.



Scheme 92 – Attempted synthesis of 226a catalysed by Bn-BOX ligand 227 and Cu(II)

Following the reaction conditions reported by Jorgensen, four new compounds were isolated but they could not be identified unambiguously. However, the ^{1}H NMR spectrum and the mass spectrum measured did not account for the desired product **226a**.

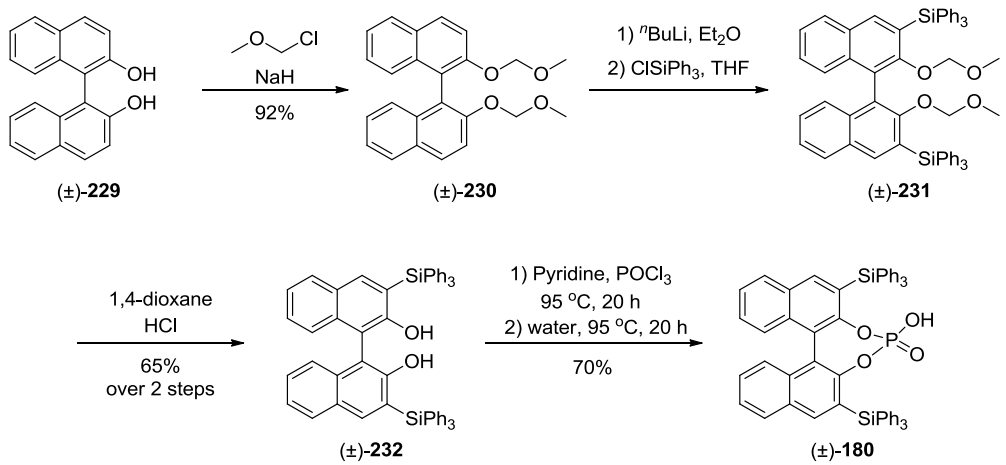


Scheme 93 – Synthesis of 226a catalysed by chiral phosphoric acid (*R*)-228

Pleasingly, following Rueping's conditions, **226a** was isolated in 45% yield and in an excellent 90% ee after the reaction was stirred for 5 days at 30 ˚C (Scheme 93).

It is worthy of note that the reaction did not proceed in the presence of *p*TSA and that (±)-**226a** had to be synthesised in the presence of (±)-**180**, synthesised in four steps and 42% overall yield from (±)-binol **229** following a literature procedure[83] (Scheme 94).

[83] Storer, I. R.; Carrera, D. E.; MacMillan, D. W. *J. Am. Chem. Soc.* **2006**, *128*, 84.



Scheme 94 – Synthesis (±)-180 from binol (±)-229

With those excellent results as a starting point for the development of an enantioselective nitro-Mannich / lactamisation cascade, optimisation studies could be undertaken.

4.3 Optimisation studies

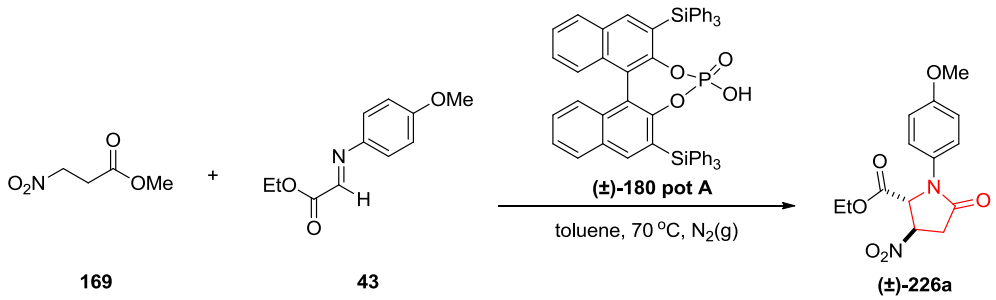
The work in this chapter has been conducted in the laboratories of the University of Oxford as well as the laboratories of Organon (newly Merck) in Newhouse, Scotland. This is important as problems linked to the provenance of the catalyst were encountered during the optimisation work. In order to allow a clear comparison of the results, the various pots of chiral phosphoric acid (*R*)-**180** used will be named, pot A (home-made in Oxford, purified by column chromatography, non-acid washed), pot B (home-made in Newhouse, purified by column chromatography, non-acid washed) and pot C (home-made in Oxford, purified by column chromatography, acid washed), and referred to in every scheme.

4.3.1 Preliminary optimisation performed in Oxford with homemade catalyst (*R*)-180 pot A

The main issue we had to tackle, in the case of this enantioselective nitro-Mannich / lactamisation cascade, was the moderate yield of the reaction. Indeed, the degree of enantiocontrol was excellent (90% ee) but the reaction was poor yielding (45%). The influence of the stoichiometry of the reagents, the temperature and the catalyst loading on the reaction were probed first.

4.3.1.1 Optimisation of the stoichiometry

The first parameter we looked at was the stoichiometry of the regents and particularly the stoichiometry of nitroester **169**, which was used in large excess (10 equivalents). Indeed, nitroester **169** has to be synthesised in three steps and, even though it can easily be recovered at the end of the reaction by flash column chromatography, a quick screen was undertaken to investigate the need of such large excess of reagent. The reaction was performed with catalyst (±)-**180** and varying amounts of nitroester **169**, and the conversion was measured by 1H NMR spectroscopy after 9 hours and 24 hours. The results are presented in Table 34.



Entry	Nitroester 169 (eq.)	Conversion (%) after 9 h	Conversion (%) after 24h
1	1 eq	8%	8%
2	2 eq	7%	19%
3	5 eq	9%	21%
4	10 eq	13%	50%

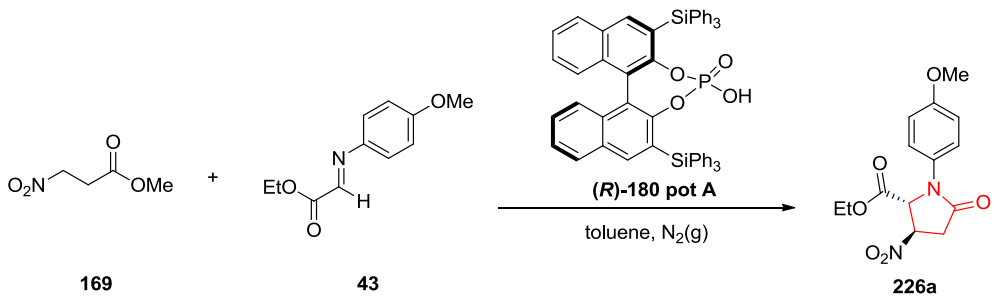
Table 34 – Optimisation of the amount of nitroester

As shown in Table 34, the formation of the desired product (±)-**180sq** is highly dependent on the quantity of nitroester **169** in the reaction mixture. Reducing the amount of nitroester from 10 equivalents to 5 equivalents, then to 1 and 2 equivalent led to a significant reduction of the conversion (from 50% to 21% and to 8%) (entries 1, 3 and 4). However, changing the stoichiometry of nitroester **169** from 2 equivalents to 5 equivalents, did not affect the yield as strongly (from 19% to 21%).

4.3.1.2 Optimisation of the temperature

Altering the temperature of the reaction was an obvious way to modify the kinetics of the reaction and maybe increase the yield. Indeed, in our previous nitro-Mannich / lactamisation cascade the

reactions were performed at 70 °C to ensure formation of the desired product in a timely fashion. In the case of an enantioselective cascade it is paramount to evaluate the effect of the temperature on the enantioselectivity, as in many cases the enantiomeric ratio decreases with increasing temperature. Accordingly, the reaction was done at room temperature, 40 °C, 70 °C and at reflux in toluene, and the yields and enantiomeric ratios obtained are reported in Table 35.



169 43 226a

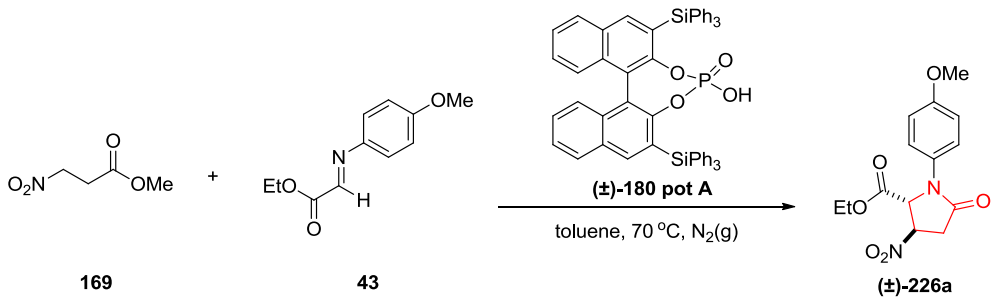
Entry	Temp. (°C)	Time (h)	yield (%)	ee (%)
1	RT	48h	traces	90%
2	40 °C	48h	44%	89%
3	70 °C	7h	50%	91%
4	reflux	4h	44%	80%

Table 35 – Temperature screen

Pleasingly, as shown in Table 35, the enantiomeric ratio was found to be relatively unaffected by the temperature and it remained constant between room temperature (entry 1) and 70 ˚C (entry 3). In refluxing toluene, the enantiocontrol was slightly impaired and an enantiomeric ratio of 80% was measured. As found in chapter 1, the temperature had a great impact on the kinetics of the reaction; at room temperature only traces of products **226a** were isolated after 48 hours, whereas 44% of product **226a** was obtained at 40 ˚C after the same period of time, and at 70 ˚C, 50% of desired pyrrolidinone **226a** was formed in only 7 hours. Accordingly, for the rest of the optimisation studies, the reactions were run at temperatures ranging from 60 ˚C to 70 ˚C.

4.3.1.3 Optimisation of the catalyst loading

Next, the influence of the catalyst loading on the yield of the reaction was assessed (Table 36). The reaction was performed as usual with a 10 mol% catalyst loading (entry 1) and this result was compared to a reaction with 20% catalyst loading (entries 2 and 3) and a reaction with 10 mol% catalyst and addition of another 10 mol% catalyst after 24 hours (entry 4).



Entry	(±)-180	Total Time (h)	yield (%)
1	10 mol%	48h	65%
2	20 mol%	48h	57%
3	20 mol%	48h	26%
4	10 mol% + 10 mol% after 24h	48h	56%

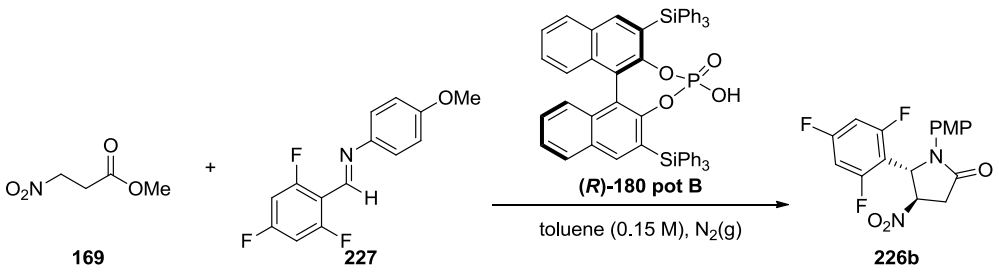
Table 36 – Catalyst loading screen

Unexpectedly, the reaction performed with a higher catalyst loading (entries 2, 3 and 4) provided the desired pyrrolidinone **226a** with a lower yield. It is also important to note that there were reproducibility issues with this reaction (compare entries 2 and 3).

4.3.2 Further optimisation studies in Newhouse with homemade (*R*)-180 pot B

4.3.2.1 Optimisation of the temperature

Concerned about the reproducibility of the reaction and the need to verify that an enantioselective cascade could be performed with imines other than **43**, a broader temperature screen (from room temperature to reflux in toluene) was undertaken with an imine bearing an electron deficient aromatic group, imine **227**. The results are presented in Table 37.



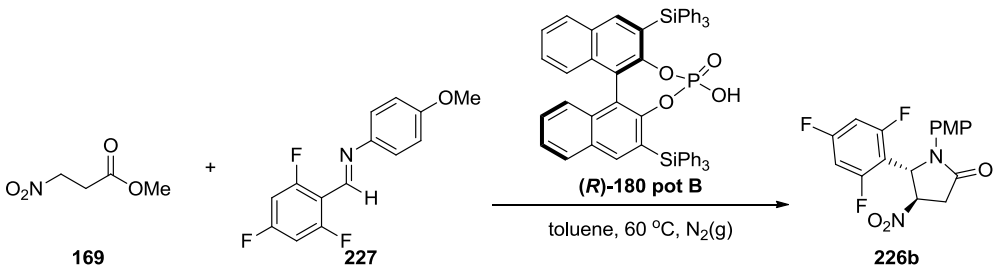
Entry	Temp. (°C)	Time (days)	yield (%)	ee (%)
1	RT	7days	2%	55%
2	30 °C	3 days	4%	55%
3	40 °C	3 days	16%	55%
4	50 °C	2 days	27%	55%
5	60 °C	2 days	18%	55%
6	70 °C	1 day	18%	55%

Table 37 – Temperature screen for imine 19

Pleasingly, in all six reactions the desired product **226b** was isolated in yields ranging from 2% (entry 1) to 27% (entry 4). As seen previously for imine **43**, the enantiomeric ratio was not affected by the temperature, and temperatures above 40 ˚C were essential for the reaction to proceed efficiently. However, the degree of enantiocontrol obtained for the reaction with imine **227** (55% ee) was fairly disappointing when compared with the best result of imine **43** (Scheme 93). The conditions of the reaction were compared to the one used with imine **43** and it was found that the concentration of the reaction had been modified (three times more concentrated). The effect of the dilution on the enantioselectivity was therefore studied.

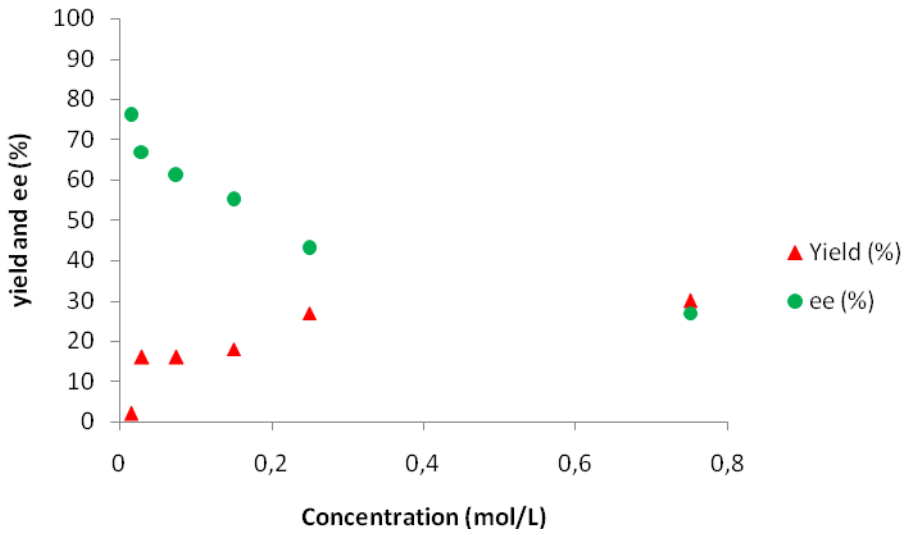
4.3.2.2 Optimisation of the concentration

In order to comprehend the influence of the concentration on the reaction, imine **227** was reacted with nitroester **169** and 10 mol% (*R*)-**180** catalyst in varying amounts of toluene, so that the concentration ranged from 0.75 mol/L to 0.015 mol/L. The results are reported in Table 38 and for a better visualisation they are shown in Graph 8.



Entry	Concentration (mol/L)	Time (h)	yield (%)	ee (%)
1	0.75	18h	27%	27%
2	0.25	18h	27%	43%
3	0.15	24h	18%	55%
4	0.075	24h	16%	61%
5	0.03	24h	16%	67%
6	0.015	48h	2%	76%

Table 38 – Influence of the dilution on the enantioselectivity

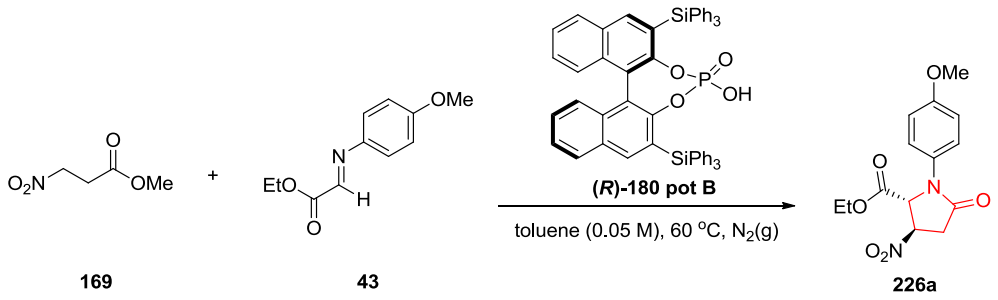


Graph 8 – Effect of the concentration on the yield and enantioselectivity of the reaction

As seen in graph 1 and as expected from the previous results, the enantiomeric ratio of product **226b** increased strongly with decreasing concentration of the reaction, from 27% ee at 0.75 mol/L (Table 38, entry 1) to 76% ee at 0.015 mol/L (Table 38, entry 6). However, the yield of the reaction had a strong tendency to decrease with decreasing concentrations (from 27% yield at 0.75 mol/L to 2% yield at 0.015 mol/L). In order to find a compromise between the yield and the enantiomeric ratio, a concentration of 0.05 mol/L was rigorously inspected in the following reactions.

4.3.2.3 Importance of the formation of the imine

The optimisation studies conducted so far were performed with preformed imine **43**. Nevertheless, the idea of developing a three component enantioselective cascade was still very attractive. Accordingly, three reactions were set up (Table 39): one where ethyl glyoxalate and *p*-methoxyaniline were added along with nitroester **169** (entry 1), one where imine **43** was preformed and purified as usually done to be used as a reference (entry 2) and a final one where ethyl glyoxalate and *p*-methoxyaniline were allowed to stir for 1 hours at room temperature, before the rest of the reagents were added (entry 3).



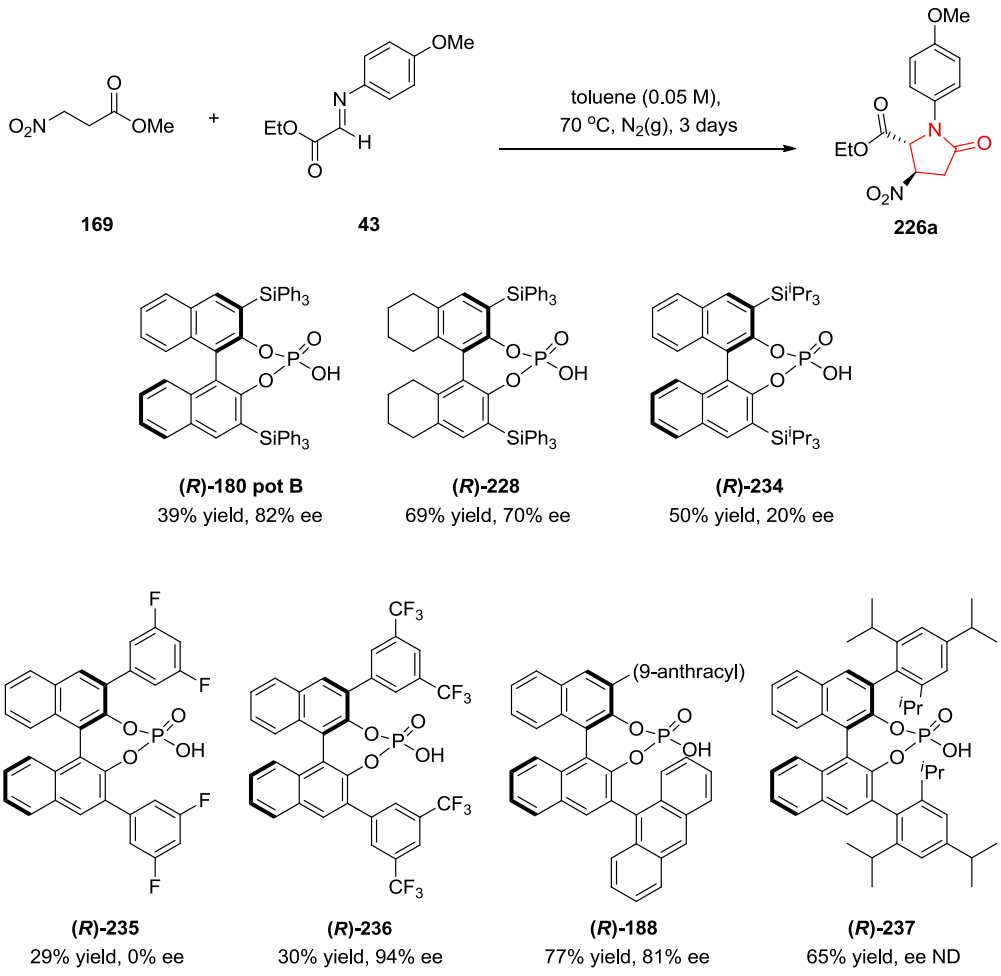
Entry	Imine 43	Conversion (%)	ee (%)
1	Formed *in situ*	21%	86%
2	Preformed purified	30%	93%
3	Preformed *in situ*	22%	37%

Table 39 – Importance of the mode of formation of imine 43

As presented in Table 39, product (±)-**226a** was isolated in all three reactions but the conversion and the enantioselectivity were different depending on the way the imine was formed. The highest conversion (30%) and enantiomeric excess (93%) was obtained for the reaction where imine **43** was synthesised and purified before reacting with nitroester **169** (entry 2). It is noteworthy that a three component one pot enantioselective cascade can be performed as well with a very degree of enantiocontrol (86% ee, entry 1). Surprisingly, preforming the imine *in situ* and reacting it without further purification with nitroester **169** led to a strong decrease in enantiocontrol (37% ee, entry 3). Accordingly, it was decided to preform and purify the imines before submitting them to the enantioselective cascade reaction.

4.3.2.4 Catalyst screens

Besides our best efforts to improve on the yield, it remained moderate in the enantioselective nitro-Mannich / lactamisation cascade. A wide catalyst screen, with a broad range of chiral phosphoric acid bearing different substituents in the 3 and 3' positions, was undertaken in order to attend to that problem while maintaining the excellent degree of enantiocontrol. Nitroester **169** and imine 43 were reacted in the presence of the various acids presented in Scheme 95 and allowed to stir at 70 ˚C for 3 days.

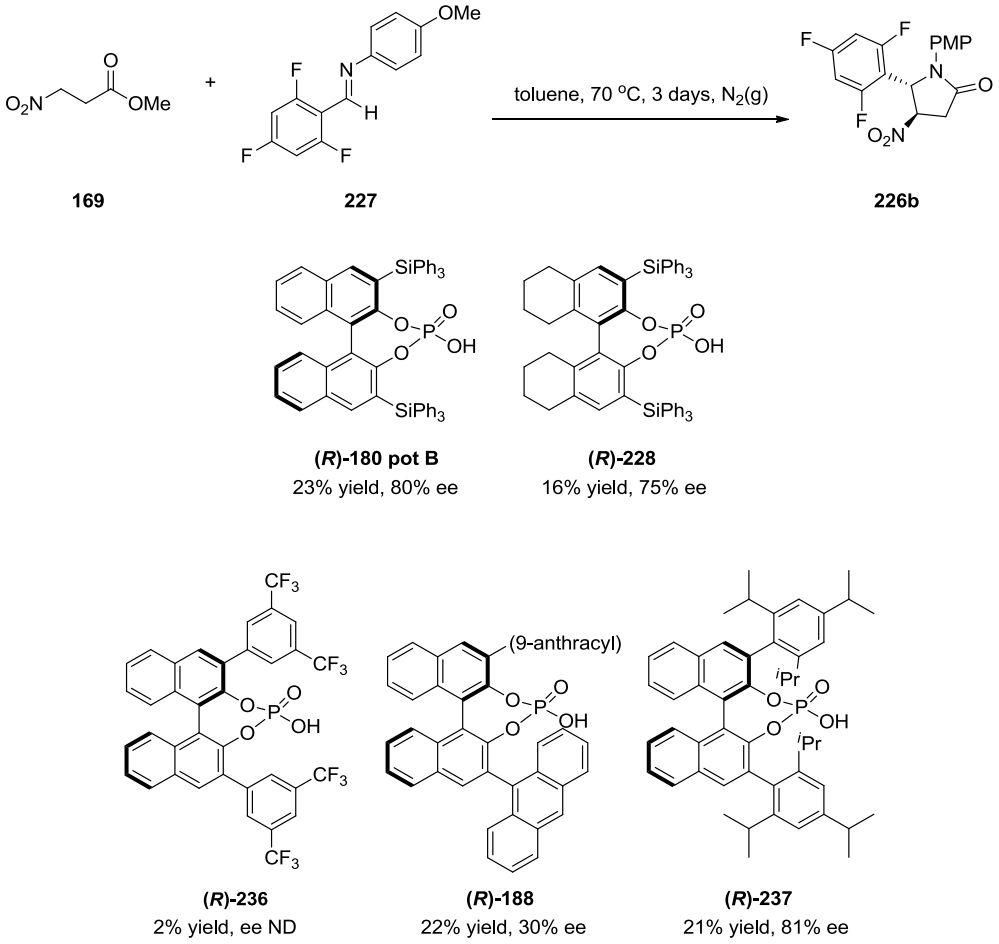


Scheme 95 – Catalyst screen for the synthesis of 226a

As presented in Scheme 95, both the efficiency of the reaction to form **226a** and its enantioselectivity were strongly influenced by the nature of the phosphoric acid, with yields ranging from 29% (with (*R*)-**235**) to 77% (with (*R*)-**188**) and enantiomeric excesses ranging from 0% (with (*R*)-**235**) to 94% (with (*R*)-**236**). Very pleasingly, catalyst (*R*)-**188**, bearing a 9-anthracyl substituent, provided **226a** with the best compromise between enantiocontrol and efficiency of the reaction with a very good

yield (77%) and a very good enantiomeric excess (81%). This result was very encouraging as it was the first optimisation study that successfully led to a strong increase in the efficiency of the cascade while maintaining a very good enantioselectivity.

However, a second catalyst screen was performed with imine **227** with the five catalysts that provided the best results in the previous screen, in order to see if the effect of the nature of the catalyst would be comparable. Accordingly, imine **227** and nitroester **169** were reacted with catalysts (*R*)-**180**, (*R*)-**228**, (*R*)-**236**, (*R*)-**188** and (*R*)-**237** and the results are presented in Scheme 96.



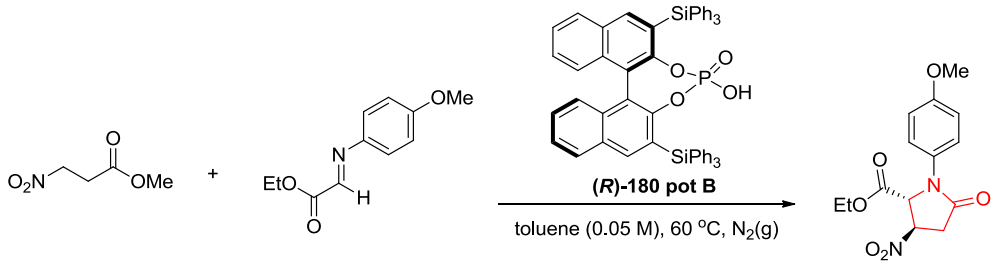
Scheme 96 – Catalyst screen for the synthesis of 226b

In all five reactions, pyrrolidinone **226b** was obtained in poor yields (from 2% to 23%) and disappointingly, catalyst (*R*)-**188**, which provided the best result in Scheme 95, enabled the formation of pyrrolidinone **226b** with poor efficiency (22% yield) and poor enantioselectivity (30% ee). The highest degrees of enantiocontrol (80% and 81% ee) were reached with catalysts (*R*)-**180** and (*R*)-**237** respectively.

By comparing the results obtained in both catalyst screens, (*R*)-**180** was selected to be the catalyst for the method.

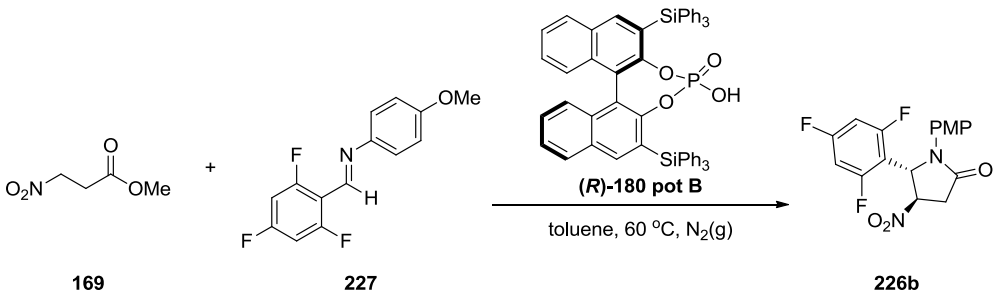
4.3.2.5 Optimisation of the catalyst quantities

A final optimisation study was undertaken to try and improve on the yield of the reaction. Imines **43** and **227** were reacted with nitroester **169** and various catalyst loadings of (*R*)-**180**, and the results are presented in Table 40 and Table 41 respectively. The concentration of 0.05 M was with respect of the catalyst.



Entry	Catalyst (*R*)-180	Conversion (%)	ee (%)
1	10 mol%	30%	93%
2	20 mol%	50%	89%
3	30 mol%	61%	90%

Table 40 – Optimisation of the amount of catalyst with imine 12



Entry	Catalyst (*R*)-180	Conversion (%)	ee (%)
1	10 mol%	18%	73%
2	20 mol%	38%	80%
3	30 mol%	12%	81%

Table 41 – Optimisation of the amount of catalyst with imine 19

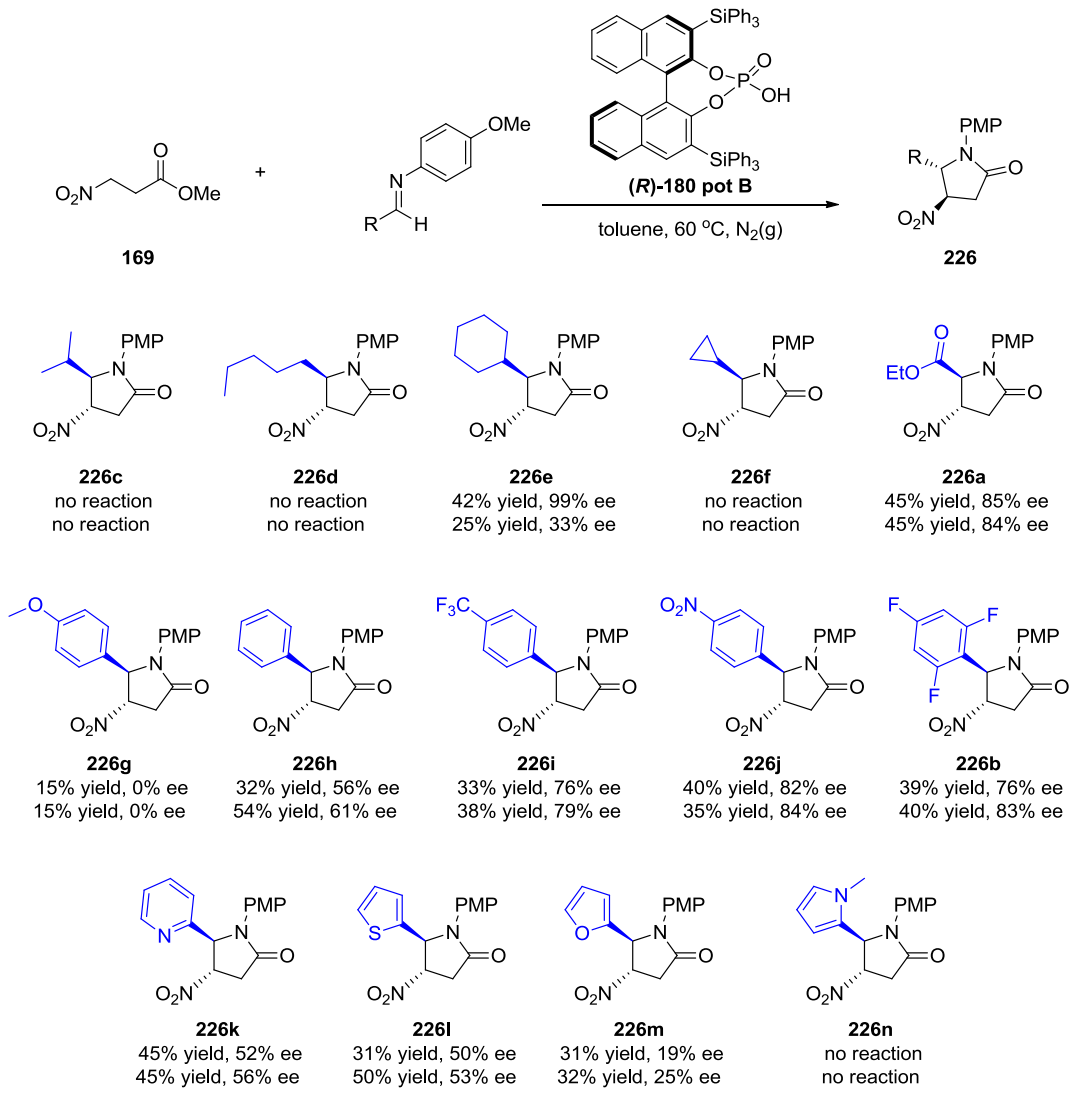
Pleasingly and unlike the results collected in our previous and related screen (Table 35), the yield of the reaction of imine **43** and nitroester **169** was strongly increased with increasing catalyst loading: 30% yield was obtained with 10 mol% catalyst (Table 40, entry 1) and 61% yield with 30% catalyst loading (Table 40, entry 3) whilst maintaining the enantiomeric excess. A similar trend was observed

with imine **227** (Table 41): the yield was increased from 18% to 38% by doubling the amount of catalyst and the enantiomeric excess was improved slightly from 73% to 80% (entries 1 and 2). Surprisingly, with 30% catalyst loading the yield of the reaction dropped to 12% (another clue of non-reproducibility of the results).

The optimisation studies revealed that the efficiency of the reaction could be improved by increasing the temperature, the concentration and the catalyst loading and by varying the nature of the acid. The various screens also highlighted that the enantiocontrol of the reaction increases with decreasing concentration and increasing catalyst loading, that it was affected by the nature of the acid and remained constant with varying temperature. With these data in hand the scope of the reaction was probed with respect to the *C*-substituent on the imine (PMP was maintained).

4.4 Initial scope of the reaction ((*R*)-180 pot B)

In order to probe the scope of the reaction with respect to the imine, 14 imines were synthesised from the condensation of *p*-methoxyaniline with various aldehydes (aliphatic, aromatic and heteroaromatic aldehydes). Each reaction was performed twice, once with 10 mol% loading and a second time with 20 mol% loading and the results are presented in Scheme 97.



Scheme 97 – First scope of the reaction

As shown in Scheme 97, out of the 14 reactions, only 4 reactions failed to provide any of the desired pyrrolidinones **226c**, **226d**, **226f** (bearing aliphatic substituents) and **226n** (bearing a *N*-methyl pyrrole substituent). The average yield of the reaction remained moderate (36%) and the enantiomeric excess varied greatly between 0% (**226g**) and 85% (**226a**). It appeared that the highest degrees of stereocontrol (70% to 85% ee) were reached with imines bearing electron deficient substituents (pyrrolidinones **226a**, **226i**, **226j** and **226b**). Product **226h**, substituted by an electron neutral phenyl group, provided a lower enantioselectivity (56% and 61% ee) and **226g** bearing an electron donating substituent was isolated as a racemic mixture. Possibly, the reactivity of the imine to the nitro-Mannich / lactamisation cascade is enhanced by electron neutral and electron rich substituents and the uncatalysed reaction proceeds faster therefore impairing the enantioselectivity. Products with heteroaromatic substituents **226k**, **226l** and **226m** were formed in moderate yields

(45%, 31% and 31% respectively) and moderate enantiomeric ratios (52%, 50% and 19% respectively). It is worth noting that the effect of doubling the catalyst loading was different in all cases; sometimes there was no effect at all (**226a**), some other times the yield and enantiomeric ratio were improved (**226h**) and finally, in some examples the yield and enantiomeric ratio were diminished (**226e**).

After studying many parameters in the reaction, probing its scope and comparing all the results obtained it is clear that the results are not reproducible and we started wondering about the real nature of the catalytic active species in the reaction.

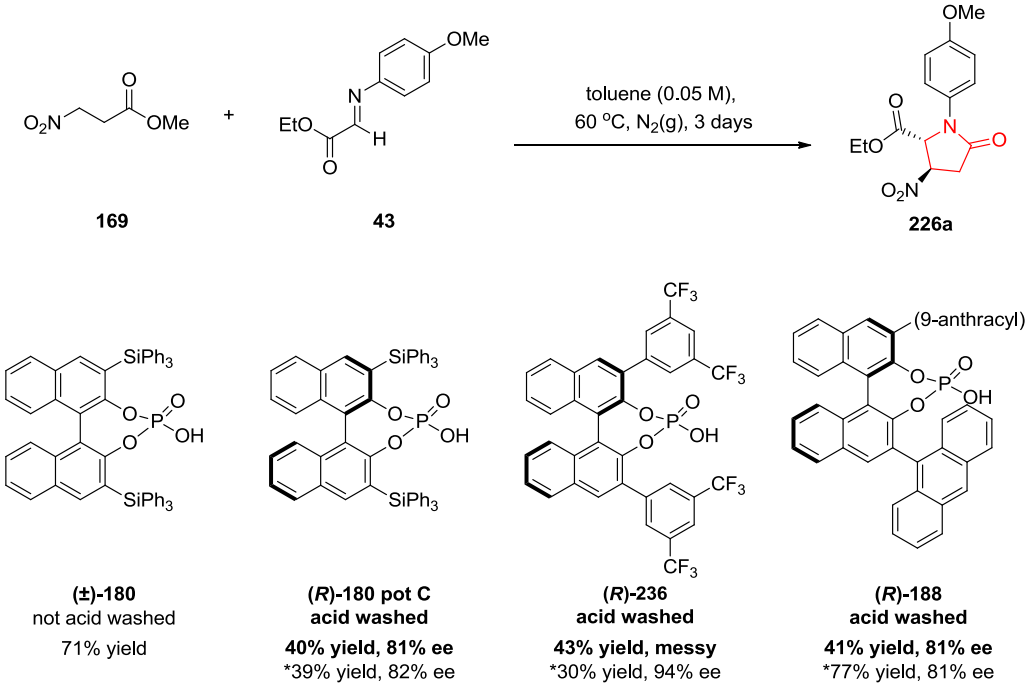
4.5 Further investigations

Several research groups working with chiral phosphoric acids reported the occurance of various metal salts contaminants formed during the the purification by column chromatography.[84] Moreover, in some cases, the reaction was actually found to be catalysed by the metal salt of the acid and not the acid itself. Indeed, those reports insist on the importance of using a catalyst that has been previously washed by a 1M aqueous solution of HCl to ensure the sole presence of the acid catalytic species. These observations are consistent with the non-reproducibility of our results and accordingly, we first repeated our reaction with acid washed chiral phosphoric acid (pot C).

4.5.1 Acid washed catalyst

As described above, in order to ensure the chiral phosphoric acids were 100% in the acid form, acid (*R*)-**180**, (*R*)-**234** and (*R*)-**188** were dissolved in dichloromethane and washed with a 1M aqueous solution of hydrochloric acid. Then, these enantiopure acid washed catalysts and non acid washed racemic (±)-**180** were reacted with nitroester **169** and imine **43** and the results are presented in Scheme 98.

[84] (a) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823; (b) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed*. **2008**, *47*, 2840; (c) Rueping, M.; Theissmann, T. M.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem. Int. Ed*. **2008**, *47*, 6798; (d) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. Adv. Synth. Catal. **2008**, *350*, 1776. (e) Shen, K.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 6008; (f) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett*, **2010**, *14*, 2189.

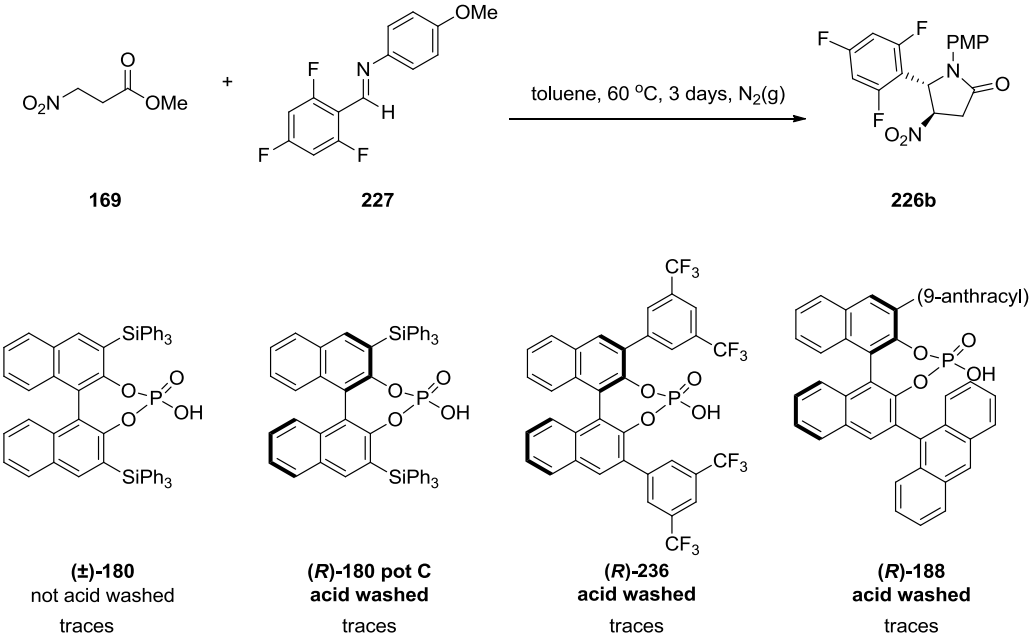


*results for comparison obtained with the non acid washed catalyst presented in Scheme 95

Scheme 98 – Catalyst screen with acid washed catalysts

Two important observations can be made from the results shown in Scheme 98: first, the non acid washed racemic catalyst (±)-**180** enabled the formation of (±)-**226a** in a very good yield (71%) and the results obtained with acid washed catalysts (*R*)-**180**, (*R*)-**236** and (*R*)-**188** are different from the one obtained previously in Scheme 95 with the non-acid washed catalyst analogues. These observations strongly suggested that the catalytic species responsible for the efficiency of the reaction and for the enantiocontrol were not the same.

Similar experiments were conducted with imine **227** and acid washed catalysts (*R*)-**180**, (*R*)-**236** and (*R*)-**188** but unfortunately, the 4 reactions only provided traces of the desired pyrrolidinone **226b** (Scheme 99).



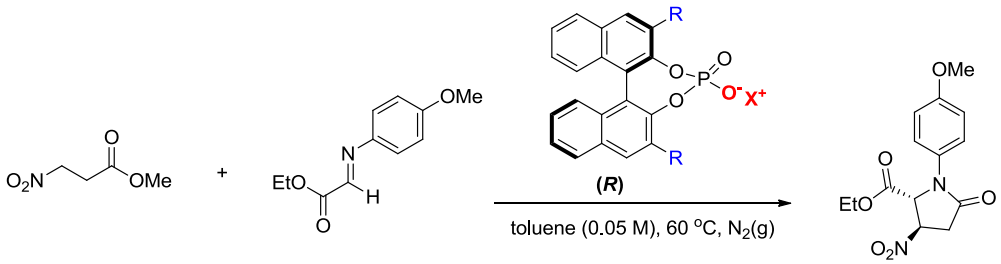
Scheme 99 – Catalyst screen with acid washed catalysts

These observations strongly suggested that the catalytic species responsible for the efficiency of the reaction and for the enantiocontrol were not the same.

Accordingly, various salts of chiral phosphoric acids (*R*)-**180**, (*R*)-**236** and (*R*)-**188** were synthesised.

4.5.2 Investigation of the nature of the catalyst

As briefly mentioned, several publications report the catalytic activity of various salts of the chiral phosphoric acids, such as the calcium salt, the sodium salt, the potassium salt and the magnesium salt, which are believed to be formed during the purification process on the column of silica gel. Several of these salts were synthesised and used in the enantioselective nitro-Mannich / lactamisation cascade. The results are presented in Table 42.



169 43 226a

Entry	R	Counter ion	yield (%)	ee (%)
1	$SiPh_3$	Acid washed	35%	86%
2	$SiPh_3$	Ca salt	54%	57%
3	anthracyl	Ca salt	19%	55%
4	*m*,*m*-bisCF_3-phenyl	Ca salt	38%	19%
5	$SiPh_3$	Na salt	-	-
6	$SiPh_3$	K salt	-	-
7	$SiPh_3$	Mg salt	32%	76%
8	$SiPh_3$	50/50 Ca salt/ acid	38%	57%
9	$SiPh_3$	50/50 Na salt/ acid	57%	63%

Table 42 – Investigation of the nature of the catalyst

The reaction of imine **43** and nitroester **169** in the presence of the sodium and the potassium salt of (*R*)-**180** failed to provide any of the desired product (entries 5 and 6). However, the reaction with the magnesium salt (entry 7) enabled the formation of pyrrolidinone **226a** in similar yield and slightly altered enantiomeric excess than the reaction with the acid washed catalyst (entry 1). Interestingly, in the reaction with the calcium salt of (*R*)-**180** (entry 2) the chemical yield was twice as good as the reaction with the acid washed catalyst, but the enantiomeric ratio was decreased significantly. These results suggested that the enantioselectivity is better controlled by the acid form of the catalyst and the efficiency by the salt. Accordingly, two other reactions were performed with a 1:1 mixture of acid and salt catalyst (entries 8 and 9). With a 1:1 mixture of sodium salt and acid form of (*R*)-**180** the desired product **226a** was formed in a gratifying 57% yield and 63% ee (entry 9).

As proposed by Rueping[85], the acid is assumed to control the enantioselective nitro-Mannich reaction by binding with the acy form of the nitroester during its reaction with the inmine *via* a Zimmerman-Traxler type intermediate to form the corresponding amine. Then it is possible that the basic phophonate salt assists the deprotection of the amine formed *in situ* and facilitates the lactamisation reaction to **226a** (Figure 17).

[85] Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.

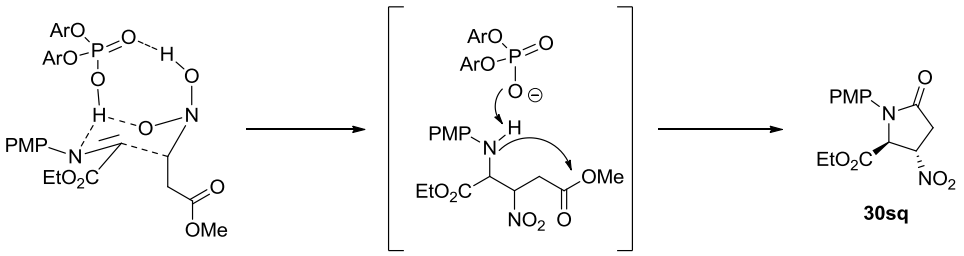
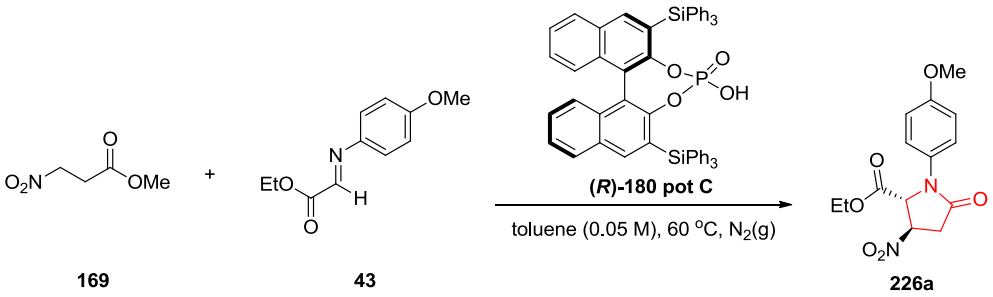


Figure 17 – Postulated role of the acid and salt catalytic species

Those results were obtained 2 weeks before the end of the "lab base" section of my DPhil and we wanted to verify the scope of the reaction with electron deficient substituents on the imine. Since the acid washed catalyst was the catalyst that was providing the highest degree of stereocontrol it was chosen to be used in the scope.

First, a quick screen was undertaken to assess the efficiency of the acid washed catalyst (Table 43). The reaction with 10 mol% catalyst loading (pot C) and 10 equivalents of nitroester **169** (entry 1) was compared with an increased catalyst loading of 20 mol% (entry 2) and a decreased stoichiometry of nitroester **169** (entry 3).



169 **43** **226a**

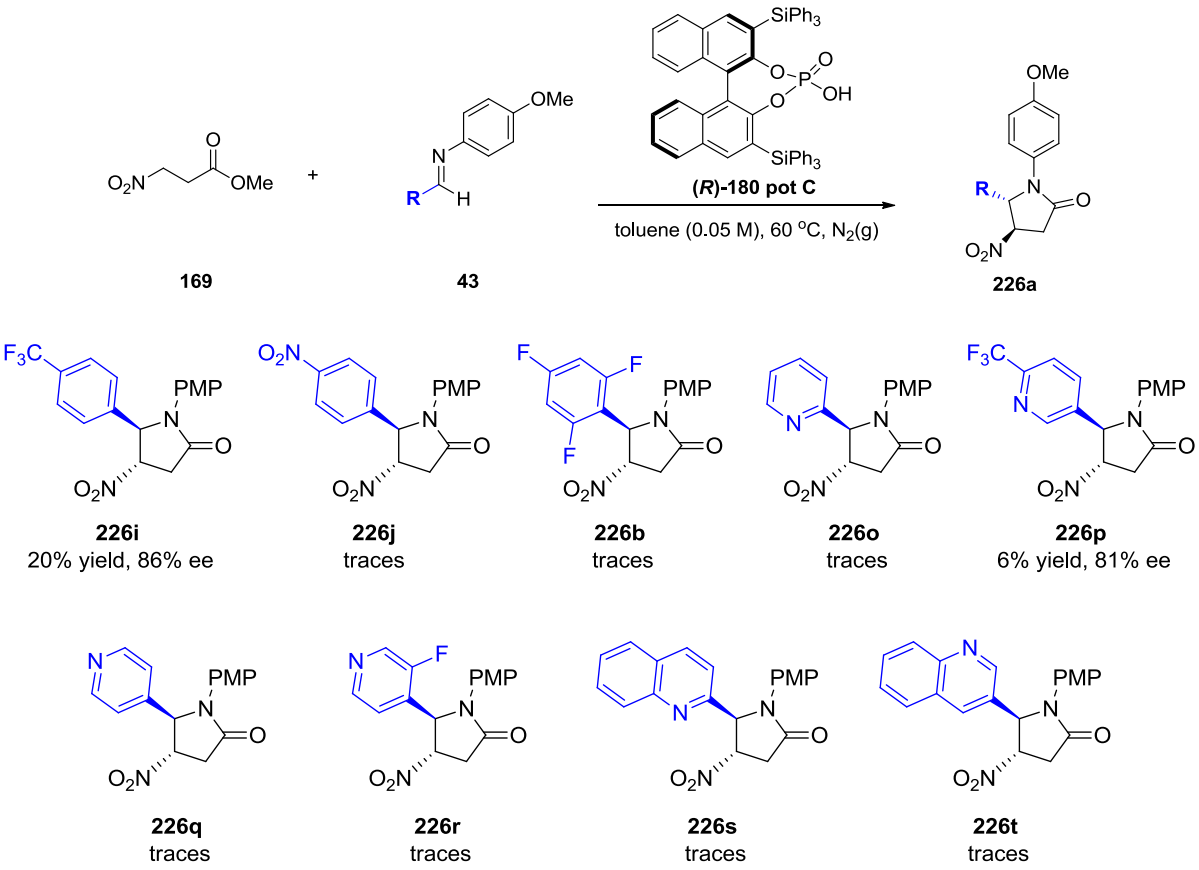
Entry	Nitroester 169	Imine 43	Catalyst (*R*)-180	yield (%)	ee (%)
1	10	1	10%	40%	81%
2	10	1	20%	31%	83%
3	5	1	10%	38%	85%

Table 43 – Optimisation of the amount of acid washed catalyst and nitroester 169

Surprisingly, increasing the catalyst loading resulted in a diminution of the chemical yield from 40% to 31% while maintaining the enantiomeric ratio. Pleasingly and for the first time, decreasing the stoichiometry of nitroester did not have any influence on the yield or the enantiocontrol. With 10 mol% catalyst loading and 5 equivalents of nitroester **169** we could probe the scope of the reaction with acid washed (*R*)-**180** and several imines bearing electron deficient substituents.

4.5.3 Reaction scope with electron deficient imines

The reaction was performed using 9 electron deficient imines. The results are presented in Scheme 100.



Scheme 100 – Scope of the reaction with acid washed catalyst and electron deficient substituents

Unfortunately, only two of the nine desired pyrrolidinones were formed in sufficient quantities to be isolated. **226i** and **226p** were formed in a disappointing 20% and 6% yield respectively but they displayed an excellent enantiomeric excess (86% and 81% ee respectively).

4.6 Conclusion

In conclusion, an enantioselective nitro-Mannich / lactamisation cascade for the synthesis of 4-nitropyrrolidinones was successfully discovered, mostly understood and partly developed. The reaction with imines bearing electron deficient substituents provided the corresponding heterocycles in excellent enantiomeric excess (80% average) and moderate chemical yield (40% average). Unfortunately, so far, the reaction is limited in scope and in lots of cases the results were not

reproducible. In the last month of my DPhil, we showed that the nature of the catalyst (acid form *vs* salt) is probably responsible for those limitations. Further work is required on this reaction to improve the chemical yield and the scope and I believe that some work around the catalyst could solve both issues simultaneously.

CHAPTER 5

Mechanistic Investigation

of

The Nitro-Mannich / Lactamisation Cascade

5.1 Context

In chapters 1, 2, 3 and 4, the nitro-Mannich / lactamisation cascade was studied extensively towards the synthesis of 4-nitropyrrolidin-2-ones. The desired 5-membered ring heterocycles were synthesised very efficiently with a wide variety of functional groups and different substitution patterns. In most cases the products were obtained with very high degrees of diastereocontrol and the work towards an enantioselective cascade, yet to be completed, allows the synthesis of pyrrolidinones with up to 93% ee.

During the course of our investigations, various questions were raised about the reaction; such as the origin of the diastereocontrol or the influence of the air on the reaction, and so on.

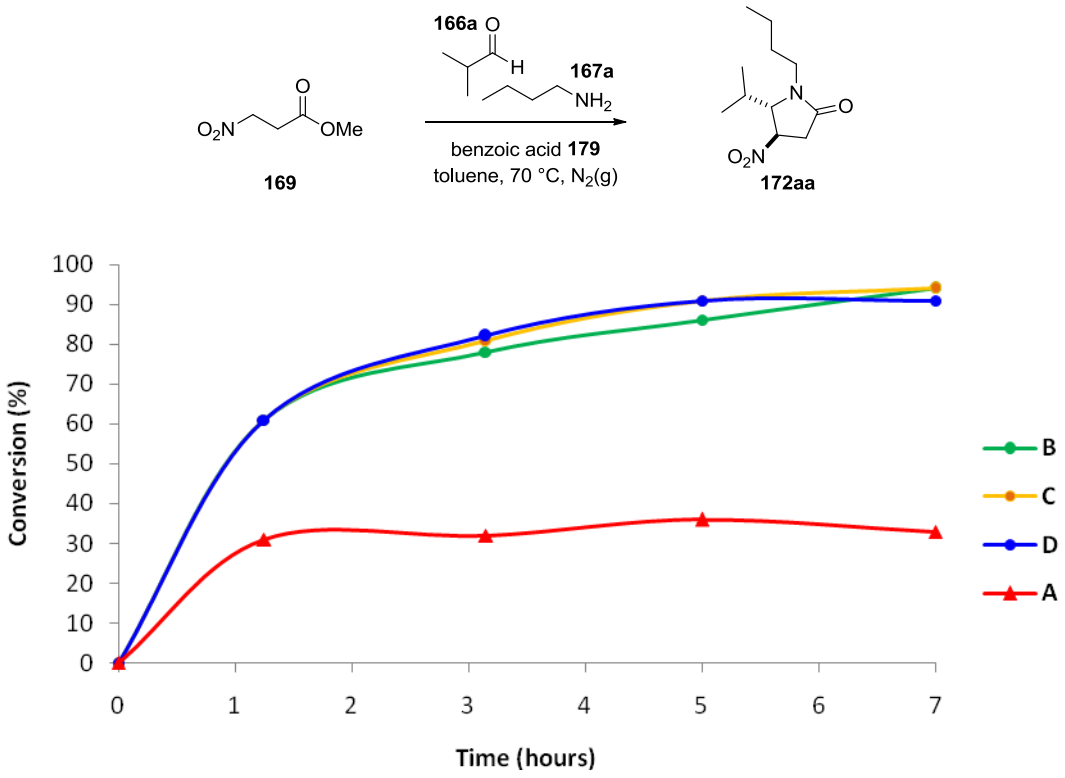
In this chapter, we describe the several investigations that were undertaken in order to gain a good understanding of the reaction mechanism and to provide insight into this cascade reaction.

First, we describe our experiment to probe and understand the role of the air on the reaction and then we will report various experiments to probe the mechanism of the nitro-Mannich / lactamisation cascade.

5.2 The influence of the air on the reaction

In the first chapter, we described the need of degassing the reaction mixture, *via* a pump/fill procedure, as it was crucial for the efficiency of the nitro-Mannich / lactamisation cascade. This finding was particularly surprising as the similar cascade reaction to form the analogous six-membered ring piperidin-2-ones were performed in water or methanol in an open vessel. In addition, the reagents that were used, nitroesters, amines **167** and aldehydes **166** are not particularly sensitive to the air or to moisture. In order to understand this specificity, we first tried to determine which component of the air was responsible for affecting the reaction system. Accordingly, the reaction of nitroester **169** with isobutyraldehyde **166a**, butylamine **167a** and benzoic acid **179** in toluene was submitted to the following reaction conditions: reaction A was not degassed and left open to the air, reaction B was degassed and pump/filled with nitrogen, reaction C was degassed and

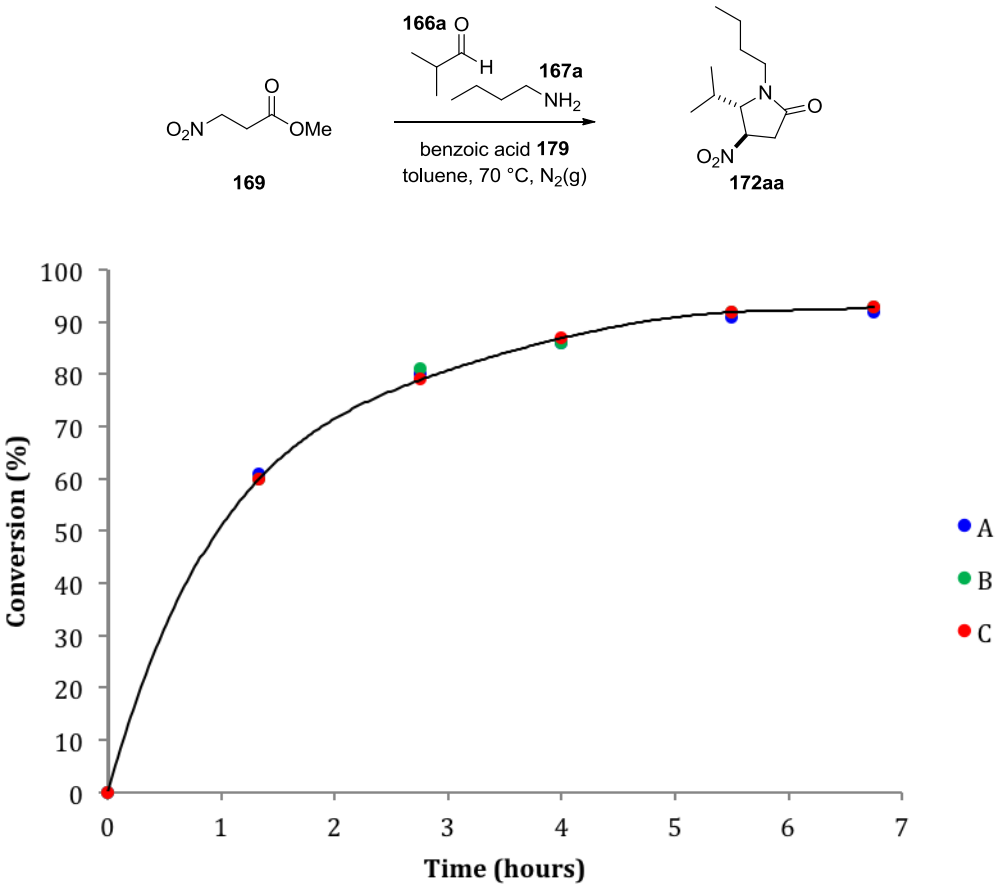
pump/filled with carbon dioxide and finally reaction D was degassed and pump/filled with nitrogen and three drops of water were added to it. The conversion of each reaction was monitored and measured by ^{1}H NMR spectroscopy over 7 hours and the results are presented in Graph 9.



Graph 9 – Finding the component of the air interfering with the cascade reaction

As shown in Graph 9, reactions B, C and D proceeded smoothly whereas reaction A stopped after about 30% conversion to the desired product. This suggested that nitrogen, carbon dioxide and water did not have any detrimental effect on the reaction. Therefore, we concluded that oxygen was the component of the air that was responsible for impairing the reactivity.

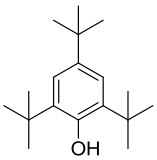
Accordingly, three new reactions were set up, degassed and purged with nitrogen (curve A), with air (curve B) and with oxygen (curve C). The advancement of the reactions was measured by ^{1}H NMR spectroscopy over 7 hours and the results are presented in Graph 10.



Graph 10 – Probing the effect of oxygen on the cascade reaction

Surprisingly, all reactions (A, B and C) proceeded smoothly and reached 93% conversion in 7 hours. The same reactions were repeated where nitrogen, air and oxygen were bubbled in the reaction mixture *via* a needle instead of using the pump/filling method employed previously. This time, the reaction under nitrogen was the only one to progress normally and the reactions where air or oxygen was bubbled through toluene stopped after 30% and 10% conversion respectively. These results confirmed that oxygen was the component of the air that was affecting the reactivity of the system and that once toluene was degassed, the rate of dissolution of the gas into toluene was very slow compared to the reaction time and that is why in Graph 10 the reaction performed normally.

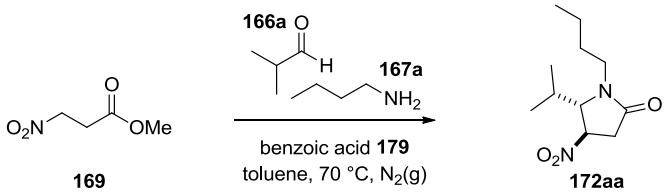
Since oxygen was found to be responsible for affecting the cascade reaction we considered the possibility of a side reaction involving a radical mechanism, taking place. Accordingly, three new reactions were undertaken and degassed: nitrogen was bubbled through reaction A, oxygen was bubbled through reactions B and C and in addition, a radical scavenger **1**, was added to reaction C.

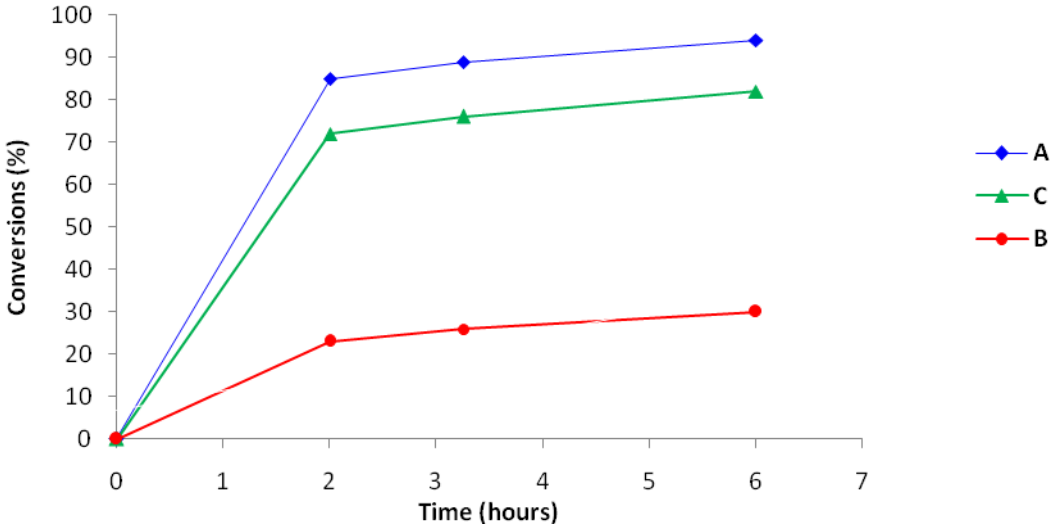


238

Figure 18 – Radical scavenger 2,4,6-tri-^{t}butylphenol 238

The conversion in each reaction was measured by ^{1}H NMR and the results are presented in Graph 11.





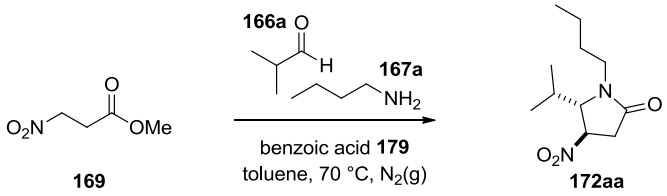
Graph 11 – Use of a radical scavenger

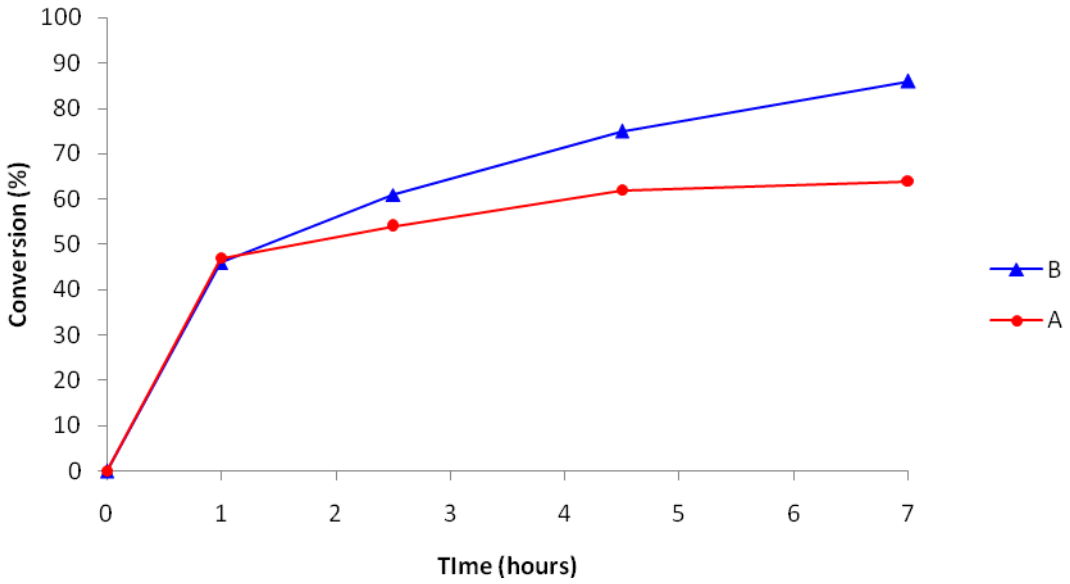
As expected, reaction A proceeded normally and reached 92% conversion after 7 hours and reaction B stalled after 25% conversion. Pleasingly, reaction C led to the desired product in 80% conversion after 6 hours. This result confirmed that oxygen was interfering with the desired cascade reaction and that, in addition, it was doing so *via* a radical mechanism since the use of a radical scavenger allowed the nitro-Mannich / lactamisation cascade to take place efficiently. However, we did not understand which component was being affected and how.

The nitro-Mannich / lactamisation cascade reaction of nitroester **169** with *p*-anisaldehyde **166b**, butylamine **167a** and benzoic acid **179** provided some new insights on this matter. This reaction was used as a model system to observe the reaction cascade by Raman spectroscopy and, as such, was performed without being previously degassed. Surprisingly, the reaction was fast and efficient, and

full conversion to the desired pyrrolidinone **172ba** was achieved in 4 hours. The reaction with isobutyraldehyde **166a** was repeated without previous degassing and the reaction stalled after **30%** conversion as typically observed. These observations were very useful as it suggested that the aldehyde **166** was the reagent of the cascade reaction that could be affected by the presence of oxygen.

Accordingly, two reactions were set up with freshly distilled isobutyraldehyde **166a** and toluene saturated with oxygen. Reaction A was run as such and in reaction B, an equivalent of freshly distilled isobutyraldehyde **166a** was added after 1 hour of reaction. The reactions conversions were monitored and measured by ^{1}H NMR spectroscopy over 7 hours and the results are presented in Graph 12.



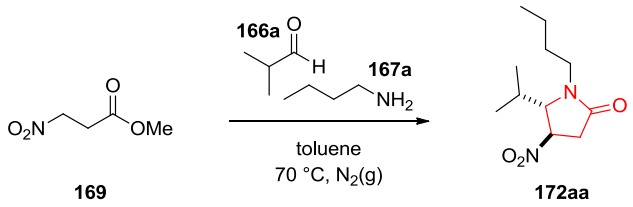


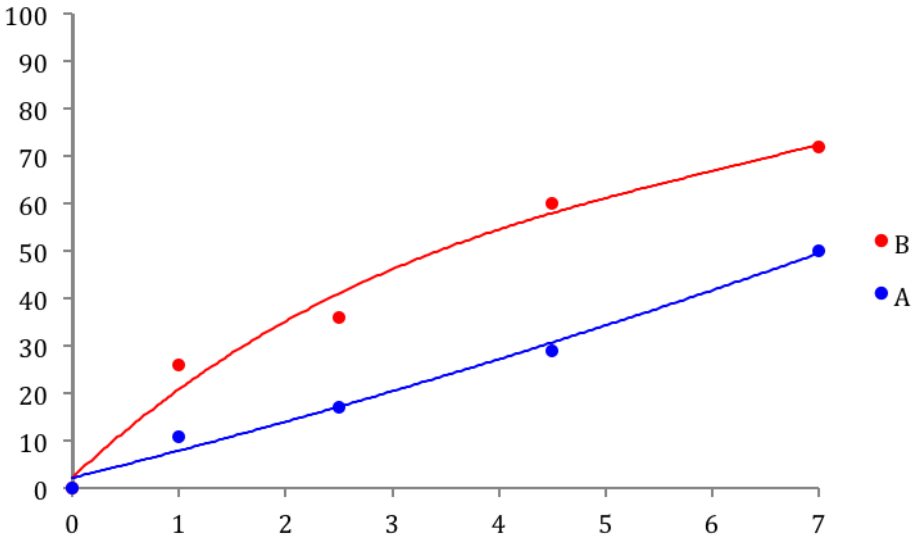
Graph 12 – Aldehyde 166a is affected by oxygen

As shown in Graph 12, reaction A stopped after 60% conversion whereas pleasingly, upon addition of another aliquot isobutyraldehyde, reaction B reached 90% conversion in 7 hours. We can conclude that oxygen is interfering with the aldehyde of the reaction *via* a radical mechanism and this prevents it from reacting in the nitro-Mannich / lactamisation cascade. Also, different aldehydes are not

affected equally; for example, isobutyraldehyde **166a** is very sensitive to the presence of oxygen whereas *p*-anisaldehyde does not seem to be affected at all. We believed that isobutyraldehyde **166a** could form a radical species that cannot be used in the cascade reaction anymore. Depending on the ease of formation of this radical the presence of oxygen would have a different impact on the nitro-Mannich / lactamisation cascade.

We also thought that the aldehyde could be oxidised to the corresponding carboxylic acid. If it was the case, and an acid is being formed, then we should see autocatalysis of the reaction. With the aim of testing this hypothesis, two cascade reactions of nitroester **169**, isobutyraldehyde **166a** and butylamine **167a** in toluene were (degassed and pump/filled with nitrogen)performed in the absence of benzoic acid. Reaction A was performed with freshly distilled isobutyraldehyde **166a** and reaction B with isobutyraldehyde **166a** saturated with oxygen. The conversions of the reactions were measured by ^{1}H NMR spectroscopy over 7 hours and the results are presented in Graph 13.





Graph 13 – Comparing the rate of the reaction with different sources of isobutyraldehyde 166a

As seen in Graph 13, reaction A was slower than reaction B. This could suggest that isobutyraldehyde in presence of oxygen was oxidised partially to the corresponding carboxylic acid and that isobutyric acid **239** acted as a catalyst in the cascade reaction, in a similar fashion to benzoic acid did.

In conclusion, we found that the oxygen of the air was responsible for affecting the nitro-Mannich / lactamisation cascade by reacting with the aldehyde **166** and forming a radical species. The aldehyde thus consumed would not be available to undergo the cascade reaction anymore. Also it was found that the efficiency of the oxidation reaction by oxygen depended strongly of the nature of the aldehyde: some, such as isobutyraldehyde **166a**, were strongly affected and others, like *p*-anisaldehyde **166b**, were not affected at all.

5.3 Studies towards a better understanding of the nitro-Mannich / lactamisation cascade

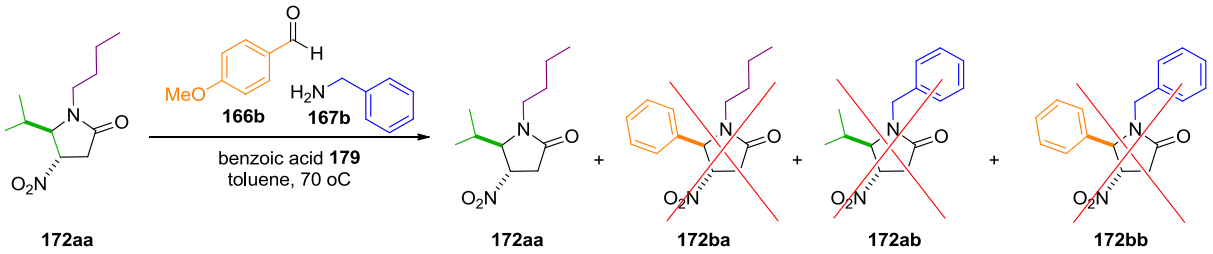
As we were first developing the nitro-Mannich / lactamisation cascade and then expanding it further, various observations were made that led us to wonder about the many aspects of the reaction. Although we gained a better understanding, a number of things reamined unclear. We were curious about the origin of the diastereocontrol, the difference of diastereoselectivity between cyclic and acyclic imines, the reason for the lower reactivity of sterically hindered reagent, etc.

5.3.1 Is the reaction under kinetic or thermodynamic control?

We first tried to establish if the diastereomeric ratio obtained in the nitro-Mannich / lactamisation cascade reaction was the result of a reaction under kinetic or thermodynamic control. In other words, was the major diastereoisomer the one that formed faster or the most thermodynamically stable diastereoisomer formed by equilibration of the acidic proton alpha to the nitro group postcyclisation?

We started by verifying that the entire cascade reaction was not reversible by performing a scrambling experiment (Scheme 101). Pyrrolidinone **172aa** was reacted with p-methoxybenzaldehyde **166b** and butylamine **167b** under the nitro-Mannich / lactamisation cascade

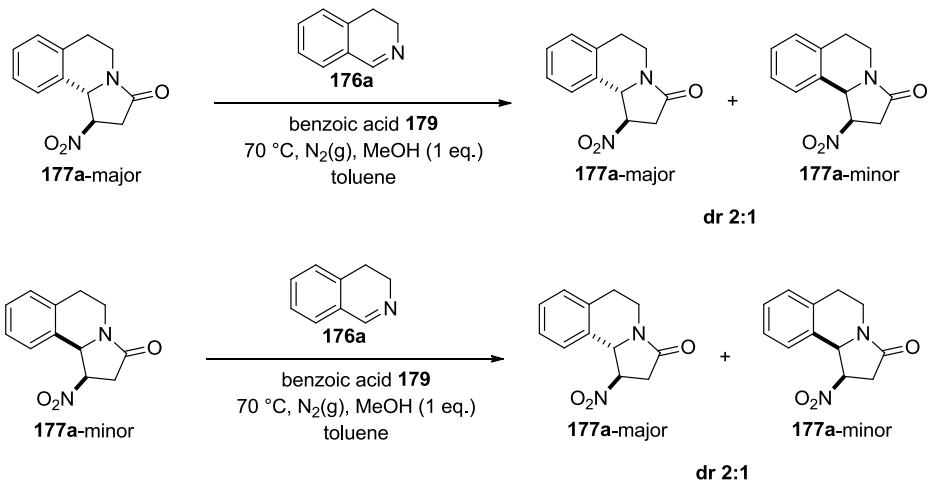
reaction conditions. If the cascade reaction were to be completely reversible we should be able to isolate a mixture of pyrrolidinones **172aa**, **172ab**, **172ba** and **172bb**.



Scheme 101 – Scrambling expriment

None of the scrambling products were formed after 24 hours at 70 ˚C and starting material **172aa** was the only pyrrolidinone isolated. This experiment concluded on the non reversibility of the full cascade reaction. Then we had to verify if the diastereoisomers could interconvert under the reaction conditions.

In the case of fused tricyclic pyrrolidinones **177**, it was an easy experiment to set up, as in the presence of benzoic acid **179**, both diastereoisomers were obtained with a low degree of diastereocontrol (2:1 dr). The two diastereoisomers of pyrrolidinone **177a** were isolated by flash column chromatography then submitted back to the reaction conditions separately (Scheme 102). As detailed in chapter 1, equilibration to the other diastereoisomer occurred but the rate of equilibration was found to be much slower (about 48 hours) than the cascade reaction (12 hours).

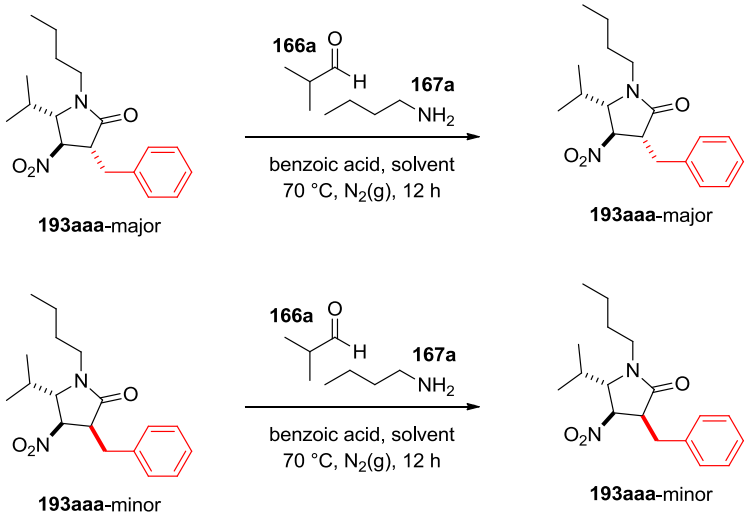


Scheme 102 – Probing the epimerization of 177a-major and minor

In chapter 1, we saw that equilibration to the thermodynamic ratio (2:1) occurs instantly with benzoic acid but the process is much slower in the absence of acid. In the case where we used chiral

phosphoric acid **180**, we believed that the high degree of diastereocontrol (14:1 for **177a**) is due to the action of acid **180** which prevents the equilibration pathway and therefore the dr observed is the result of the reaction under kinetic control with little erosion by equilibration *post*-reaction. For acyclic imines, the dr was found to be the same with or without acid (benzoic acid **179** or chiral acid **180**) and constant over time. This suggests that in the case of acyclic imines the thermodynamic ratio and the kinetic ratio are the same.

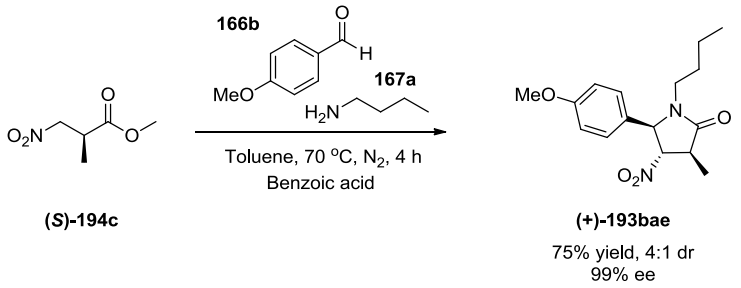
In the case of fully substituted pyrrolidinones, the two diastereoisomers of **193aaa**, *trans/trans* major and *trans/cis* minor were isolated and resubmitted to the reaction conditions separately (Scheme 103).



Scheme 103 –193aaa-major and minor do not interconvert

Even after stirring at 70 °C for seven days there was no evidence of epimerisation.

With the aim of probing the presence of possible equilibration reactions occuring alongside the cascade reaction, enantiopure methyl 2-(*S*)-methyl-3-nitropropanoate **194c** was submitted to the nitro-Mannich / lactamisation cascade with *p*-anisaldehyde **166b**, butylamine **167a** and benzoic acid **179** in toluene at 70 °C (Scheme 104).



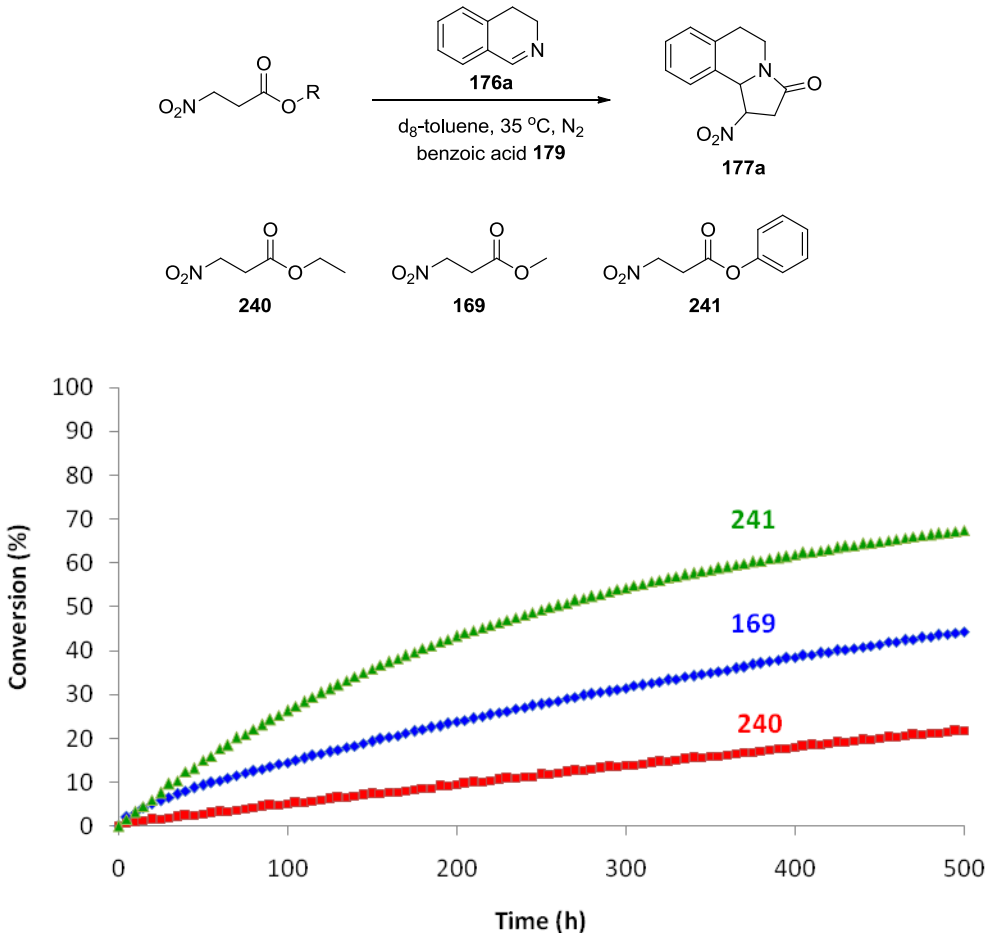
Scheme 104 – Cascade reaction with single enantiomer (*S*)-194c

Subjection of (*S*)-**194c** to simulated reaction conditions afforded (+)-**193bae** in >99% ee: racemization was not occuring at any point in the reaction pathway between **194c** and **193bae** (Scheme 104).

The reactions performed so far provided us with some interesting insights into the nitro-Mannich / lactamisation cascade but we were lacking hard evidence explaining the origin of the diastereocontrol in the case of fully substituted nitro-pyrrolidinones. Accordingly, we then decided to try and determine which one of the nitro-Mannich reaction or the lactamisation was the rate determining step.

5.3.2 What is the rate determining step?

The cascade reaction was first thought to be the result of a slow and reversible nitro-Mannich reaction followed by a fast and irreversible lactamisation, as 5-membered rings are usually formed very rapidly. However, further studies were undertaken, using cyclic imine **176a** as a model substrate, to establish which one of the nitro-Mannich or the lactamisation reactions was the rate determining step. Three nitroesters **169**, **240** and **241** bearing different ester groups (ethyl **240**, methyl **169** and phenyl **241**) were synthesised and reacted with 3,4-dihydroisoquinoline **176a** and benzoic acid **179** in deuterated toluene in an NMR tube at 35 °C. The conversion to **177a** was measured by ^{1}H NMR spectroscopy at 10 minute intervals over 8 hours and the results are presented in Graph 14.



Graph 14 – Investigating the rate determining step

As shown in the graph, the reaction speed varied strongly with the ester substituent: the reaction with **240** (ethyl) was twice as slow as the reaction with **169** (methyl) and three times slower than the reaction with **241** (phenyl). Hence, the rate increases with decreasing size or increasing reactivity of the ester moiety. By assuming that exchanging ethyl for methyl or phenyl does not significantly affect the pK_a of the carbon bearing the nitro group, these results suggest that lactamisation is rate determining. It is therefore reasonable that the origin of diastereocontrol for fully substituted nitro-pyrrolidinones (particularly in the monocylic series) lies in the favourable pseudo-equatorial positioning of the substituents during the lactamisation step and not during the nitro-Mannich reaction, which we suspect is reversible. Also, a rate determining lactamisation reaction and a reversible nitro-Mannich reaction would explain the lack of reactivity of sterically bulky reagents. The steric bulk would prevent the slow lactamisation from occuring and the nitro-Mannich reaction equilibrium would be displaced towards the entropically favoured starting materials.

5.4 Conclusion

In this chapter, we found that aldehydes **166** could be sensitive to the presence of oxygen in the solvent toluene as they could be converted to radical species and therefore become unavailable to react in the cascade reaction. It was also concluded that in the case of mono-cyclic pyrrolidinones **172,** the high degree of diastereoselectivity is due to the fact that the thermodynamic ratio is the same as the kinetic ratio, whereas for fused tricyclic products **177**, the thermodynamic and kinetic ratios are different and the diastereocontrol depends on the occurence of an equilibration *post*-cyclisation. Moreover, for fully substituted pyrrolidinones **193** the diastereocontrol is likely to originate during the rate determining irreversible lactamisation step of this reaction cascade, and not during the reversible nitro-Mannich step. Finally, the fact that the lactamisation is the rate determining step agrees perfectly with the lack of reactivity with bulky reagents.

CHAPTER 6

A Formal Synthesis

of

The Natural Product Slaframine

6.1 The target: Slaframine

Slaframine **242**, a toxic indolizidine alkaloid produced by the fungus *Rhizoctonia leguminicola*, is responsible for producing profuse salivation in cattle. *Rhizoctonia leguminicola*, usually infests members of the *Leguminosae* family, and causes black spot diseases of red clover, commonly known as "black patch".[86] The initial symptoms of the poisoning, excessive and uncontrolled salivation[86], gave slaframine its name[87] (Icel. *Slafra*, to slaver). Continued exposure to the metabolite can cause extensive liver damage and eventual death. Slaframine was first identified[88] in 1965 and originally wrongly assigned[85] as 1-acetoxy-6-aminooctahydroindolizidine **243** (Figure 19). The structure was revised in 1968 to 1-acetoxy-6-aminooctahydroindolizidine **242** (Figure 19).[89] It is thought that slaframine **242** may be metabolised in the liver and can hyper sensitize smooth muscles to the action of acetylcholine.[87] Consequently, slaframine, or an analogue, could be used in the treatment of conditions arising through cholinergic dysfunction. Also, by stimulating pancreatic secretion, slaframine could alleviate the symptoms of cystic fibrosis.[90] Since it can only be produced in small quantities from a surface culture of *Rhizoctonia leguminicola*, slaframine has received a strong interest from the synthetic community. The core structure of slaframine is constituted of a 6,5 ring system and it occurs naturally as (-)-slaframine **242**.

[86] (a) Byers, J. H.; Broquist, H. P. *J. Dairy Sci.* **1961**, *44*, 1179. (b) For a review, see Croom, W. J.; Hagler, W. M.; Froetschel, M. A.; Johnson, A. D. *J. Anim. Sci.* **1995**, *73*, 1499. For various studies, see (c) Hibbard, B.; Peters, J. P.; Chester, S. T.; Robinson, J. A.; Kotarski, W. J.; Croom, W. J.; Hagler, W. M. *J. Anim. Sci.* **1995**, *73*, 516. (d) Hibbard, B.; Moseley, W. M.; Robinson, J. A.; Boucher, J. F. *J. Anim. Sci.* **1995**, *73*, 526. (e) Chapa, A. M.; Fernandez, J. M.; Thompson, D. L.; Templeman, R. J.; Berro, L. F.; Croom, W. J.; Hagler, W. M. *J. Anim. Sci.* **1995**, *73*, 3673. (f) Froetschel, M. A. *J. Dairy Sci.* **1995**, *78*, 2395. (g) Streeter, M. N.; Froetschel, M. A.; Croom, W. J.; Hagler, W. M. *J. Anim. Sci.* **1995**, *73*, 3103.

[87] Aust, S. D.; Broquist, H. P.; Rinehart, K. L. *J. Am. Chem. Soc.* **1966**, *88*, 2879.

[88] (a) Raney, D. P.; Smalley, E. B.; Crump, M. H.; Strong, F. M. *Nature* **1965**, *205*, 203. (b) Aust, S. D.; Broquist, H. P. Nature **1965**, *205*, 204. (c) Whitlock, B. J.; Rainey, D. P.; Riggs, N. V., Strong, F. M. *Tetrahedron Lett.* **1966**, 3819.

[89] Gardiner, R. A.; Rinehart, K. L.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639.

[90] Aust, S. D. *Biochem. Pharmacol.* **1969**, *18*, 929.

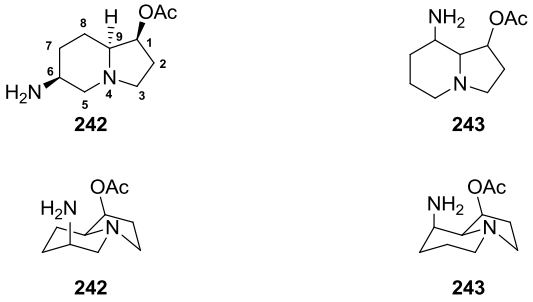
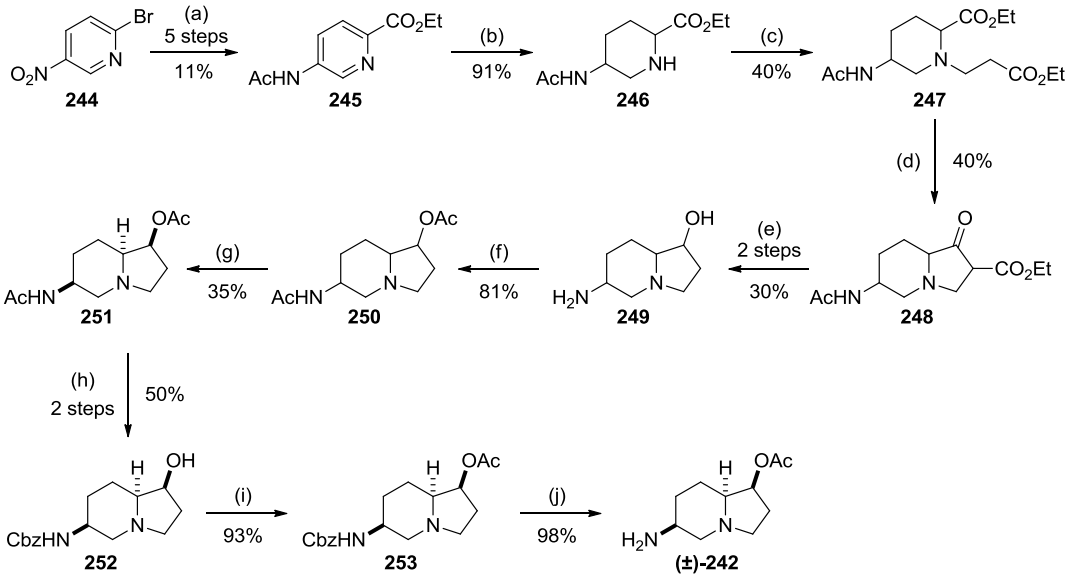


Figure 19 – Structure of slaframine 1

6.2 Previous syntheses of slaframine 242

The first total synthesis of (±)-slaframine **242** was published by Rinehart *et al* in 1970 (Scheme 105).[91] Starting from 2-bromo-5-nitropyridine **244**, a catalytic reduction of the pyridine ring, followed by a Dieckmann condensation gave rise to the 6,5 ring structure **248**. The synthesis of the desired target was completed in 0.06% yield over 16 steps. It is worth noting that the lack of stereocontrol in this synthesis resulted in the need to separate the mixture of the four possible diastereoisomers of indolizidine **249**. The desired diastereoisomer, whose NMR and IR data matched those of slaframine **242**, accounted for 35% of the mixture **250**. Even though this synthesis was lengthy and low yielding it constituted the first total synthesis of slaframine **242**.

[91] Cartwright, D.; Gardiner, R. A.; Rinehart, K. L.; *J. Am. Chem. Soc.* **1970**, *92*, 7615.

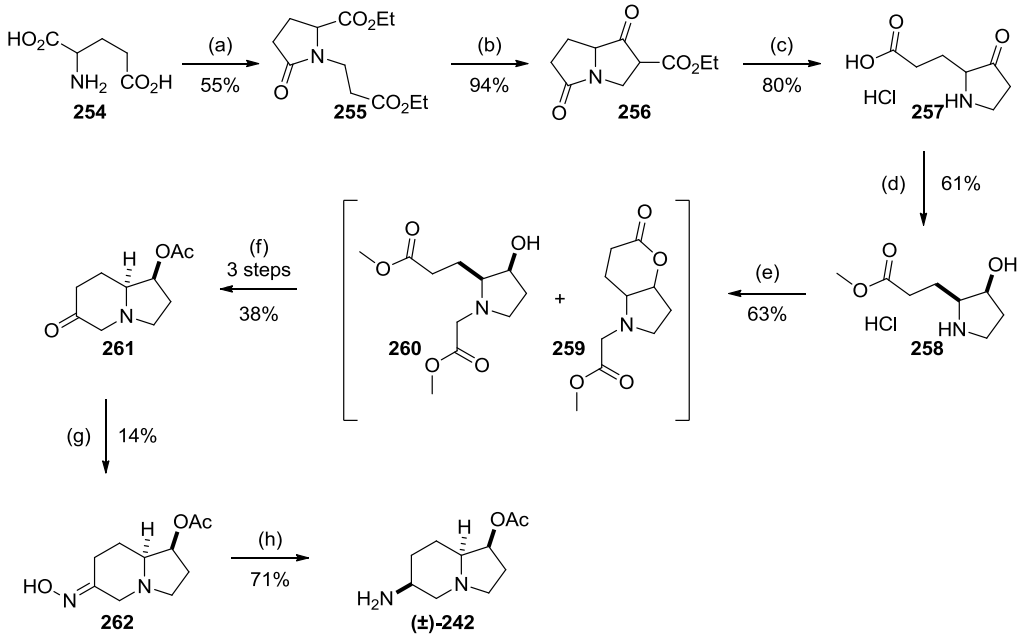


(a) i) CuCN; ii) H_3O^+; iii) EtOH / H_2SO_4; iv) PtO_2 / EtOH; v) Ac_2O (b) 50 psi H_2 (c) ethyl acrylate, EtOH, 2 days(d) KO^tBu, toluene (e) i) 8M HCl, 100 °C; ii) $NaBH_4$ (f) Ac_2O (g) separation of the 4 diastereoisomers by chromatography (h) i) hydrazine hydrate, reflux, 3 days; ii) benzyl chloroformate (i) Ac_2O. (j) HBr / AcOH

Scheme 105 - Synthesis of racemic slaframine by Rinehart *et al*

Gensler *et al* published in 1973 the first diastereoselective synthesis of (±)-slaframine **242** (Scheme 106).[92] Starting from (L)-(+)-glutamic acid **254**, the 6,5 core structure was constructed by two subsequent Dieckmann cyclisations. The relative stereochemistry in the molecule was set in two different steps *via* a similar platinum-catalyzed hydrogenation in acidic media, on ketone **257** and oxime **262**. In both cases, addition of H_2 to the least hindered face of the molecule was favoured, leading to the desired stereochemistry of (±)-slaframine **242**. This total synthesis proceeded in 10 steps and 0.6% overall yield.

[92] Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848.

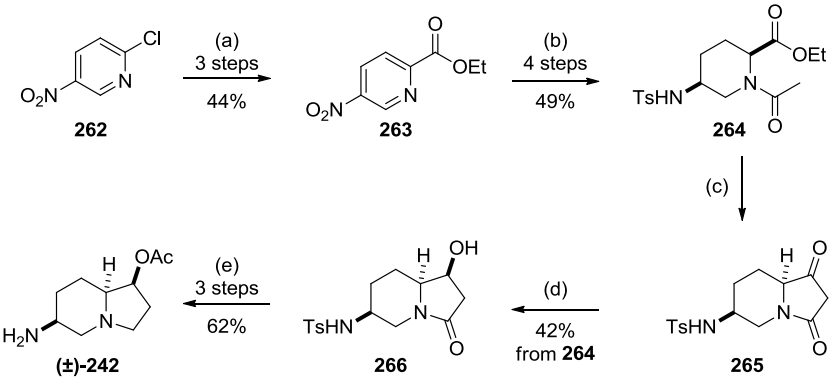


(a) i) acrylonitrile, EtOH, H_2SO_4, reflux (b) NaOEt, EtOH (c) HCl, 75 ^oC, 6h (d) PtO_2, H_2, MeOH, 1 atm, 3 days (e) methyl bromoacetate, Na_2CO_3, MeOH (f) i) NaH, benzene; ii) HCl, reflux; iii) Ac_2O, pyridine (g) $NH_2OH.HCl$, pyridine, EtOH (h) PtO_2, HCl, H_2, MeOH.

Scheme 106 - Synthesis of racemic slaframine 1 by Gensler *et al*

These early syntheses were not sufficiently efficient in terms of step count and overall yield to supply sufficient quantities of slaframine for biological assays. However, in 1984, Harris *et al* published a much improved route towards slaframine **242** from commercially available 5-chloro-nitropyridine **262** (Scheme 107).[93] Here, the key step utilised a potassium hydride mediated cyclisation of *N*-acetylpipecolate ester **264** to construct the 5-membered ring. The exclusive *cis* relationship at C-6 and C-9 is set during a catalytic reduction of the picolinate ester **263** and it is retained during the cyclisation process. The stereochemistry of C-1 was established *via* a stereoselective reduction of the ketone **265** using L-Selectride. Finally, (±)-slaframine **242** was synthesised in 12 steps and a good 5% overall yield.

[93] Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681.



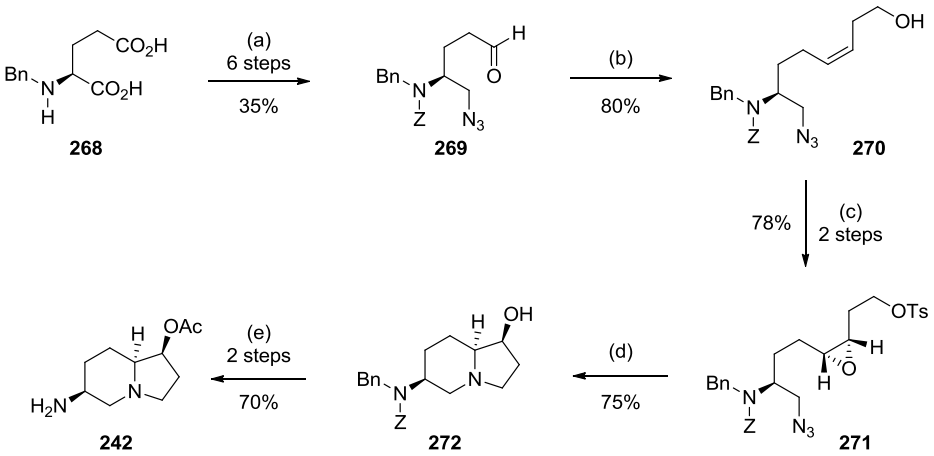
(a) i) Sodium diethyl malonate; ii) H_2SO_4, CrO_3, 70 °C; iii) EtOH, benzene, Dowex 50W x 8 (H^+ form) (b) i) H_2(3 atm), Pd/C, EtOH, 7h; ii) TsCl, pyridine; iii) H_2, PtO_2, AcOH, Ac_2O; iv) Ac_2O (c) KH (d) L-Selectride (e) i) BH_3, THF; ii) Na, NH_3; iii) AcOH, HCl

Scheme 107 - Synthesis of racemic slaframine 1 by Harris *et al*

In 1991, the absolute configuration of (-)- slaframine **242** was confirmed, first by Pearson *et al*.[94] then by Cha *et al.*[95], as both groups published the first enantioselective syntheses of the indolizidine alkaloid.

The approach adopted by Pearson *et al* revolved around a cascade reaction as the key step of the synthesis (Scheme 108).[94] The amine functionality, formed *in situ* from the reduction of the enantiomerically pure azido epoxide **271**, afforded an epoxide ring opening followed by a SN^2 alkylation and thus, allowed the construction of the 6,5 core structure, very efficiently and in one step. Finally, acetylation of the alcohol moiety of **272** and subsequent deprotection of the amine afforded (-)-slaframine **242** in 12 steps and an excellent 11.5% overall yield.

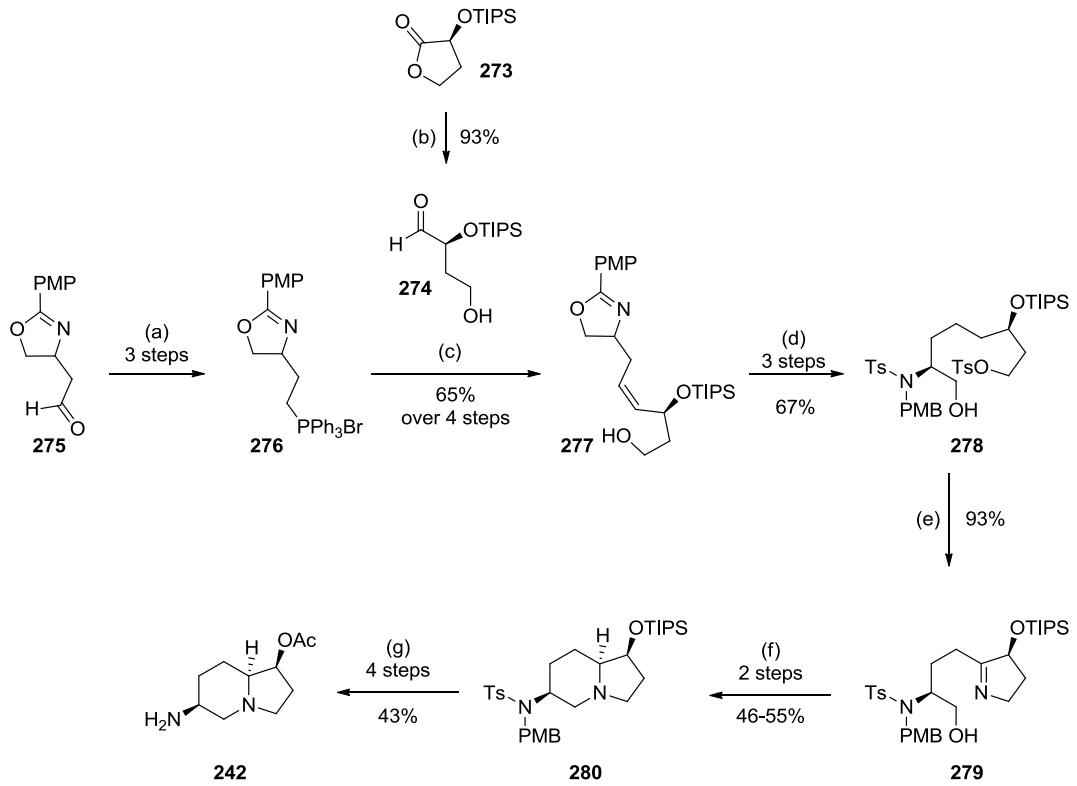
[94] Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976.
[95] Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469.



(a) i) $PhCH_2O_2Cl$, $NaHCO_3$, H_2O, 23 °C, 18 h, 71%; (ii) BH_3.THF (3 eq), THF, 0 °C, 1 h; 23 °C, 18 h, 70%; iii) TBSCl, pyridine, cat. DMAP, DCM, 0-23 °C, 12 h, 85%; iv) Ph_3P, $Et_2OCN{=}NCO_2Et$, $(PhO)_2P(O)N_3$, THF, 23 °C, 48 h, 93%; v) n-Bu_4NF, THF, 23 °C, 6h, 96%; vi) $(COCl)_2$, DMSO, NEt_3, DCM, -78 °C, 2 h, 92%. (b) $Ph_3P^+(CH_2)_3OH\ Br^-$, $KN(SiMe_3)_2$ (2 eq), THF, 0 °C, 2 h; Me_3SiCl (1 eq); -78 °C, 1 h; 23 °C, 1 h; 1M HCl, 23 °C, 1h; 80% overall (c) i) *m*CPBA, DCM, 23 °C, 3h, 91%, separation by preparative HPLC of the 1:1 mixture of diastereoisomers; ii) pTsCl, pyridine, cat. DMAP, -10 °C, 24 h, 86% (d) 10% Pd/C (5 wt %), H_2 (1 atm), EtOH, 23 °C, 24 h; filter, add K_2CO_3, reflux 18 h, 75%. (e) i) Ac2O, pyridine, 23 °C, 18h, 90%; ii) 10% Pd/C (100 wt %, 10 mol % Pd), H_2 (1 atm), EtOH, 23 °C, 4h, 78%.

Scheme 108 - Synthesis of (-)-slaframine 1 by Pearson *et al*

The synthesis designed by Cha *et al* involved a Wittig reaction between the enantiomerically pure aldehyde **274** and ylide **276** (Scheme 109).[95] The key step of the synthesis is an intramolecular azide [2+3] dipolar cycloaddition to construct the 5-membered ring as imine **279**. Subsequent reduction and ring closure, followed by various functional group modifications afforded (-)-slaframine **242** in 14 steps and a very good 8% overall yield.

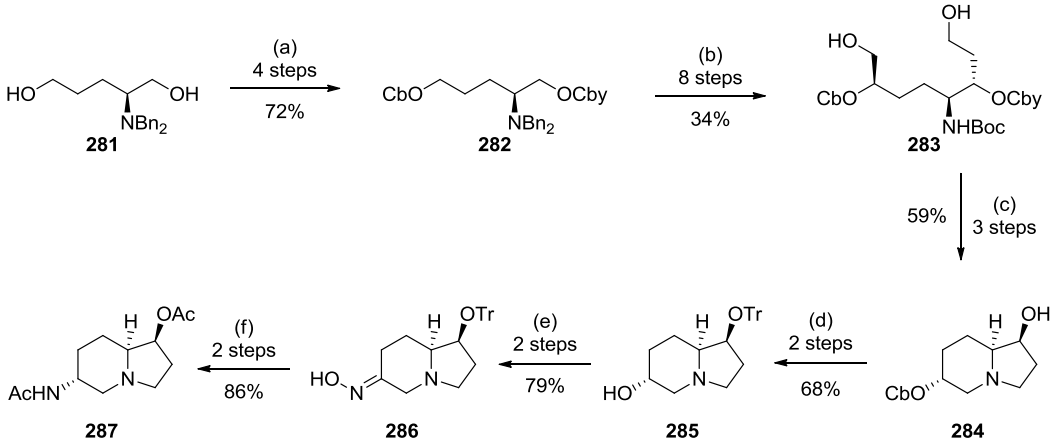


(a) i) $NaBH_4$, MeOH; ii) a) TsCl, Et_3N, cat. DMAP, DCM; b) 10 eq LiBr, $NaHCO_3$, DMF, 70 °C; iii) PPh_3, CH_3CN, reflux (b) DIBAL-H, THF (c) $KN(SiMe_3)_2$, -78 °C; then DIBAL-H reduction of (3*S*)-3-[(triisopropylsilyl)oxy]dihydrofuran-2(3H)-one, -78 °C, 1h (d) i) TsCl, Et_3N, cat. DMAP, DCM; ii) 5 eq DIBAL-H, THF, 0 °C, 1h; iii) *N*-tosyl-*N*-methylpyrrolidine perchlorate, DCM, 0 °C, 1h (e) 5 eq NaN_3, DMF, 60 °C; toluene, reflux. (f) i) MsCl, Et_3N, DCM, 0 °C; ii)a) $NaBH_4$, EtOH, 0 °C; b) K_2CO_3; c) reflux. (g) i) CAN, H_2O-CH_3CN (1:15); ii) n-Bu_4NF, THF; iii) Na, NH_3-THF; iv) HCl; AcOH, HCl

Scheme 109 - Synthesis of (-)-slaframine 1 by Cha *et al*

The most recent synthesis, by Hoppe *et al*, in 2007, utilises an enantiomerically pure amine **281** and highly stereoselective lithiation and substitution reactions to set the stereochemistry at the three stereocenters (Scheme 110).[96] A deprotection of the amine **283**, followed by two *N*-alkylations enabled the formation of the 6,5 rings. The correct stereochemistry at the C-6 position was obtained by reducing oxime **286** by hydrogenation from the *exo*-face. A final bis-acetylation afforded (-)-(*N*)-acetylslaframine **287** in 21 steps and 6.6% overall yield.

[96] Hoppe, D.; Gottschalk, K.; Guarnieri, W.; Frehlich, R. *Synthesis* **2007**, *13*, 1984.



(a) i) Et_3N, DMAP, TBSCl, DCM, 0 °C to 23 °C , 48 h; ii) NaH, THF, reflux, 1 h, CbyCl, reflux, 16 h; iii) TBAF, RT, 72h; iv) NaH, THF, reflux, 1 h, CbCl, reflux, 16 h (b) i) ^{s}BuLi / (-)-sparteine, Et_2O,-78 °C, 7 h; ii) ethylene oxide, -78 °C; iii) $BF_3.OEt_2$, -78 °C to 20 °C, 14 h; iv) ^{s}BuLi / (-)-sparteine, -78 °C, 7 h,; v) MeOC(=O)Cl, , -78 °C to 20 °C, 14 h; vi) DIBAL-H, THF, 0 °C, 2 h; vii) Pd/C, H_2, MeOH, 14 h at 20 °C, 5 h at 65 °C; viii) Boc_2O, Et_3N, MeOH, 3 h at 40 °C, 14 h at 20 °C. (c) i) MsCl, Et_3N, DCM, -20 °C, 14 h; ii) TFA, DCM, 20 °C, 14 h; iii) K_2CO_4, MeOH, 65 °C, 14 h (d) i) PPh_3Cl, DBU, DCM, 20 °C, 48 h; ii) DIBAL-H, THF, 2 h at -78 °C, 14 h at 20 °C. (e) i) $(COCl)_2$, DCM, -78 °C, DMSO, 5 h at -78 °C, Et_3N, 1 h at -78 °C, 1 h at 20 °C; ii) $HONH_2$.HCl, pyridine, EtOH, 4 h at 80 °C, 16 h at 20 °C. (f) i) PtO_2, H_2, EtOH, HCl, 20 °C, 14 h; ii) Ac_2O, pyridine, 20 °C, 2 h.

Scheme 110 - Synthesis of (-)-acetylslaframine by Hoppe *et al*

The interest of slaframine **242** by the synthetic community[97] is probably due to its 6,5-core structure, ideally suited to the development of new methodologies and common to several indolizidine alkaloids.[98] In this context we decided to tackle the construction of the 6,5 ring system of slaframine **1** and to propose a new synthesis.

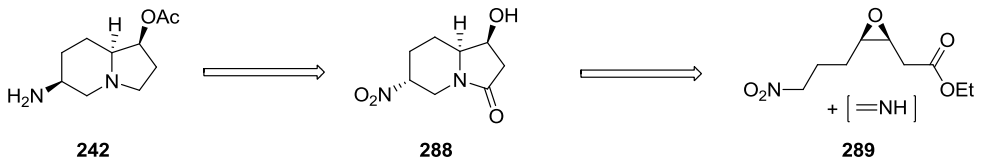
6.3 Our approach and proposed retrosynthesis

Multicomponent cascade reactions are particularly useful in total synthesis as they significantly shorten the step count. The amine functionality and the indolizidine backbone of slaframine **242**

[97] For the other syntheses see: (a) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065. (b) Dartman, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechel, A. *Liebigs Ann. Chem.* **1988**, 695. (c) Bennett, R. B.; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580. (d) Shono, T.; Matsumura, Y.; Katoch, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368. (e) Bennett, R. B.; Choi, J. R.; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 5437. (f) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976. (g) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977. (h) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802. (i) Sibi, M. P. ; Christensen, J. W.; Li, B.; Renhowe, P. A. *J. Org. Chem.* **1992**, *57*, 4329. (j) Hua, D. H.; Park, J. G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144. (k) Knight, D. W.; Sibley, A. W. *Tetrahedron Lett.* **1993**, *34*, 6607. (l) Wasserman, H. H.; Vu, C. B. *Tetrahedron Lett.* **1994**, *35*, 9779. (m) Kim, N.S.; Kang, C. H.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3489. (n) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. (o) Szeto, P.; Lathbury, D. C.; Gallagher, T. *Tetrahedron Lett.* **1995**, *36*, 6957. (p) Stockmann, R. A.; Szeto, P.; Thompson, S. H.; Hadley, M. S.; Lathbury, D. C.; Gallagher, T. *Synlett.* **1996**, 853. (q) Knight, D. W.; Sibley, A. W. *J. Chem. Soc.* **1997**, 2179. (r) Kang, S. H.; Kim, J. S.; You, J. *Tetrahedron Lett.* **1998**, *39*, 9047. (s) Dong, H. Q.; Lin, G. Q. *Chin. Chem. Lett.* **1998**, *9*, 999. (t) Sibi, M. P.; Christensen, J. W.; Li, B.; *J. Org. Chem.* **1999**, *64*, 6434. (u) Carretero, J.C.; Gómez Arrayás, R. *Synlett.* **1999**, 49. (v) Comins, D. L.; Fulp, A. B. *Org. Lett.* **1999**, *1*, 1941. (w) Pourashraf, M.; Delair, P.; Rasmussen, M.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966.(x) Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951.

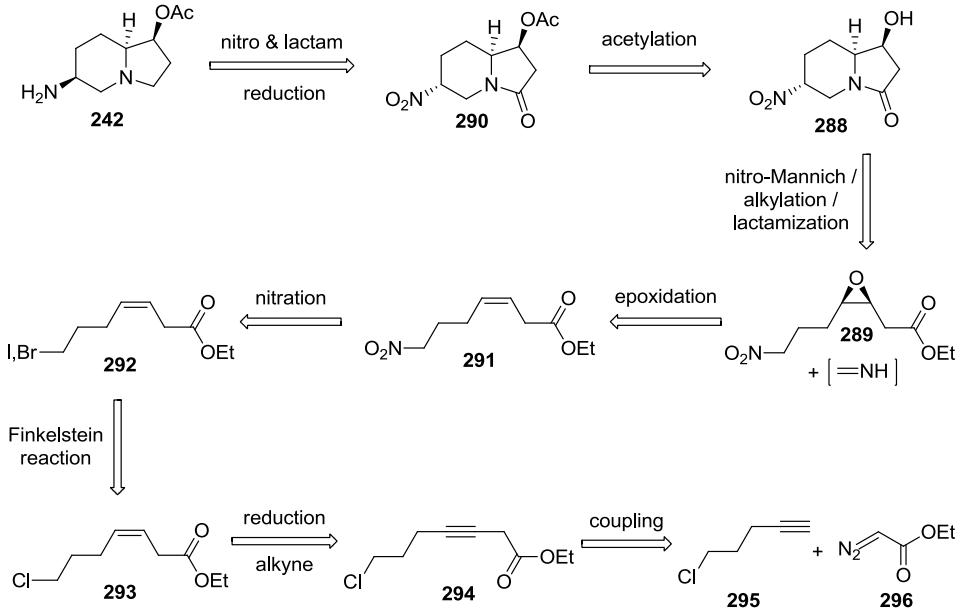
[98] http://www.scripps.edu/chem/baran/images/grpmtgpdf/Richter_May_06.pdf

make it ideally suited to formation *via* a nitro-Mannich cyclisation cascade. Therefore, our proposed retrosynthesis of slaframine **272** was designed around a key intermediate **289** bearing a terminal nitro-group, a central epoxide and a terminal ester moiety. The 6,5 ring system could then be constructed, in one pot, *via* a nitro-Mannich / epoxide ring opening / lactamisation cascade (Scheme 111).



Scheme 111 – Proposed key step towards slaframine 242

The synthesis of the key epoxide **289**, in racemic form, was envisaged in 5 steps from 5-chloropentyne **295** and ethyl diazoacetate **296**, *via* well precedented and documented chemical transformations. These included an alkyne coupling, a reduction of alkyne **294** to the *cis*-alkene analog **293**, a Finkelstein reaction, a nitration and finally a *syn*-epoxidation (Scheme 112). It was suspected that a stereoselective epoxidation might be successfully achieved under Shi catalytic system conditions.



Scheme 112 – Proposed retrosynthesis slaframine 242

Subsequently, a nitro-Mannich / epoxide opening / lactamisation cascade could afford the desired bicycle structure. First, the nitro-Mannich / epoxide opening would lead to the 6-ring. The

stereochemistry at the ring junction C-9 and at C-1 bearing the alcohol functionality would be fixed by the geometry of the epoxide and the stereospecificity of the epoxide opening. Indeed, the amine, formed *in situ* from the nitro-Mannich reaction, would open the *cis*-epoxide *via* a backside attack, typical of a SN^2 mechanism. Then, this would immediately be followed by an irreversible lactamisation to form the 5-ring. The stereochemistry of C-6, bearing the nitro-group, is believed to be fixed by equilibration *post* cyclisation and should adopt an equatorial position.

An inversion of configuration at the carbon atom bearing the nitro group was anticipated to occur during the catalytic hydrogenation; the reduction of the nitro group to the amine functionality, with catalytic palladium, proceeds *via* an oxime intermediate, the least hindered face of the oxime will approach the surface of the catalyst and thus, providing the desired diastereoisomer required for the synthesis of (-)-slaframine **242**.

Finally, a hydride reduction of the lactam **290**, followed by an acetate protection of the alcohol moiety would give rise to (-)-slaframine **242** in 9 steps overall from commercially available 5-chloropentyne **295**.

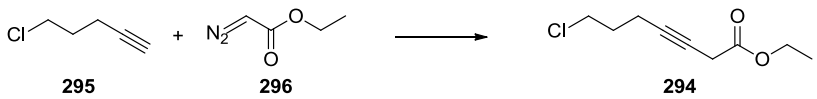
6.4 Synthesis

6.4.1 Synthesis of the key intermediate 289

6.4.1.1 Synthesis of ethyl-7-chlorohept-3-yonate 294[99]

In the literature, two main procedures were described to access the desired alkyne **294**. One article reported the use of a catalytic amount of copper iodide, and the other, the use of boron trifluoride. Both conditions were tested and, in our hands, the reaction with copper iodide provided a much higher yield (62 % vs 12 % yield) as shown in Table 44 (entries 1 and 2). Moreover, in this case, equimolar quantities of both reagents were employed instead of an excess (2.3 eq) of the relatively expensive alkyne **295**.

[99] Mizugaki, M.; Fukuyama, H.; Sakamoto, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1978**, *26*, 2417.



295 296 294

Entry	295	296	Catalyst	Solvent	Scale	Yield
1	1.0 eq	1.0 eq	CuI (5 %)	CH_3CN	0.5 g	62 %
2	2.3 eq	1.0 eq	$BF_3.Et_2O$, BuLi	THF	0.5 g	12 %
3	1.0 eq	1.0 eq	CuI (5 %)	CH_3CN	2.0 g	68 %
4	1.0 eq	1.5 eq	CuI (5 %)	CH_3CN	3.0 g	90 %
5	1.0 eq	1.5 eq	CuI (5 %)	CH_3CN	10.0 g	91 %
6	1.0 eq	1.5 eq	CuI (5 %)	CH_3CN	20.0 g	91 %

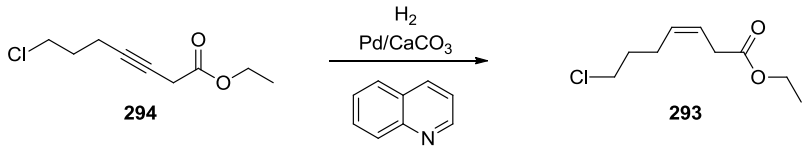
Table 44 – Optimization towards alkyne 294

The copper catalyzed reaction was found to be reproducible, scalable and by increasing the amount of diazoacetate to 1.5 equivalents, the yield could be greatly improved to 90% (entry 4). Ethylchlorohept-3-yonate **294** was isolated in 91% yield on a 20 g scale, after purification by flash column chromatography (entry 6).

Although this reaction has been reported a long time ago, its mechanism is not fully understood. However, two hypotheses can be made. On the one hand, we could postulate that the reaction proceeds *via* a copper (I) mediated loss of nitrogen, forming a copper-carbene intermediate, which then undergoes C-H insertion to give the required product. On the other hand, copper (I) could first insert into the C-H, thus providing a carbon nucleophilic enough to react with ethyl diazoacetate.

6.4.1.2 Synthesis of ethyl chloro-7-hept-3-enonate 293

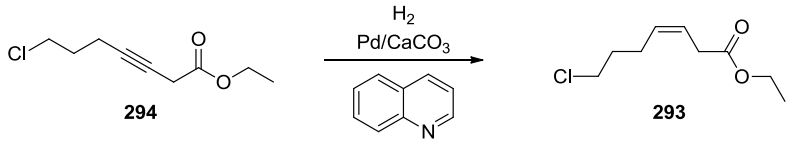
The reduction of alkyne **294** to the *cis*-alkene analog **293** was first attempted under Lindlar reaction conditions (Scheme 113).[100] The Lindlar reduction is well described in the literature for the partial hydrogenation of an alkyne to the corresponding *cis*-alkene **293**, using a partially poisoned palladium catalyst, typically poisoned by lead or barium sulphate.



Scheme 113 – Lindlard reduction of alkyne 294

[100] Lindlar, H.; Dubuis, R. *Org. Synth*. **1973**, *Coll. Vol. 5*, 880.

Accordingly, the reaction was first attempted with palladium on calcium carbonate poisoned by lead (Table 45, entries 1 and 2). Unfortunately, in the presence or in the absence of quinoline, no reaction was observed. Then, a reduced formed of palladium on calcium carbonate, presumably more active, was tried (entries 3-8). Pleasingly, in about 12 hours, full conversion was observed and the corresponding alkene **293** was isolated in 90% yield. The yield dropped to 75% and the reaction time was doubled by scaling up the reaction from 200 mg to 1.0 g. Warming up the reaction to 35 °C significantly increased the reaction rate. Nevertheless, on a 3 g scale, at 35 °C, four days and several addition of palladium (between 2 and 4 times as dictated by the progress of the reaction) were necessary to reach full conversion and a disappointing 50% yield.

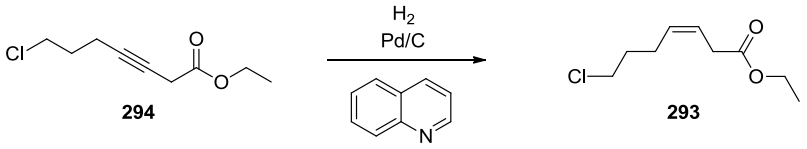


Entry	Scale 294	$Pd/CaCO_3$	Quinoline	T(°C)	Solvent	Yield
1	0.20 g	10 %, poisoned by lead	50 µL	RT	Pet. ether	-
2	0.10 g	10 %, poisoned by lead	-	RT	Ethyl acetate	-
3	0.15 g	10 %, Reduced	4 µL	RT	Hexane	90 %
4	0.20 g	10 %, Reduced*	4 µL	RT	Pet. ether	90 %
5	1.00 g	10 %, Reduced*	20µL	RT	Pet. ether	80 %
6	1.00 g	10 %, Reduced*	20 µL	RT	Ethyl acetate	75 %
7	1.00 g	10 %, Reduced*	20 µL	35 ˚C	Hexane	75 %
8	3.00 g	10%, Reduced*	60 µL	35 ˚C	hexane	50 %

*For those experiments, several additions of Pd (between 2 to 4 times after TLC analysis) were necessary to reach full conversion.

Table 45 – Optimization towards alkene 293 with $Pd/CaCO_3$

We decided to consider different sources of palladium. Palladium on carbon is not usually used to perform partial *syn* hydrogenation of alkyne functionality as over reduction to the corresponding alkane is common. Nevertheless, it was tried (Table 46), at room temperature and in presence of quinoline. While in hexane only low conversion was observed after 48 hours (Table 46, entry 1), in ethanol (alcohols are often the solvents of choice for hydrogenation) full conversion to alkene **293** was reached in 8 hours, without traces of over-reduction.



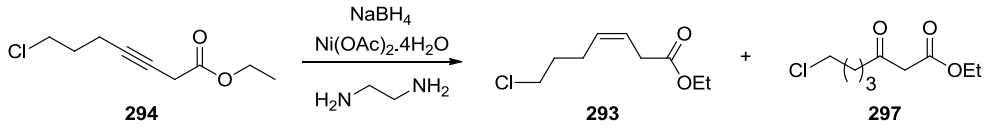
Entry	294	Quinoline	T (°C)	Solvent	Conversion	E/Z ratio
1	0.10 g	25 µL	RT	hexane	30 % (48 h)	-
2	0.10 g	25 µL	RT	EtOH	100 % (< 8 h)	3/1
3	0.10 g	-	RT	EtOH	100 % (12h)	-

Table 46 – Optimization towards alkene 293 with Pd/C

Unfortunately and a little surprisingly, the olefin was obtained with a 3:1 ratio in favour of the undesired *E* diastereoisomer. The reaction was monitored closely and it was noticed that, if initially mostly the *Z* isomer was formed, upon completion of the reaction, the product equilibrated to the more thermodynamically stable *E* isomer. Since the reaction was quite fast (30 min to 120 min) and the reaction time varied drastically with the scale, other reduction methods were investigated[101].

Various examples in the literature described the use of nickel boride as a powerful reagent for the syn selective reduction of alkyne to alkene.[102] Nickel boride is generated *in situ* from the reaction of sodium borohydride with a nickel (II) salt.

The reaction was first performed using $Ni(OAc)_2.4H_2O$ in ethanol (Scheme 114). Pleasingly, the desired *Z*-isomer was isolated exclusively. Nevertheless, the yield of the reaction was moderate (41%) due to the formation of a side product. The diketone side product **297** was isolated in significant quantities presumably through interaction of the acetate ligand on the nickel with the C-C triple bond



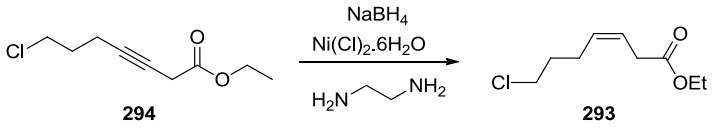
Scheme 114 - Reduction of 294 with nickel boride using nickel acetate

Accordingly, $Ni(OAc)_2.4H_2O$ was replaced by $Ni(Cl)_2.6H_2O$ (Scheme 115) and the desired product was isolated in 70% yield as the *Z*-olefin exclusively. Further optimisation studies revealed that the presence of ethylene diamine in the reaction mixture was crucial to prevent any over-reduction to

[101] Benjamin Brash, Part II thesis, « Towards the total synthesis of slaframine.

[102] (a) Augustine, R. L. "Catalytic Hydrogenation", Marcel Dekker, New York, N. Y., **1965**, *86*, 101, p. 46. (b) Eliel, E. L.; Allenger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis", Interscience, New York, N. Y., **1965**, p. 119. (c) Siegel, S. J. *Am. Chem. Soc.* **1953**, *75*, 1317.

the corresponding alkane: it acts as a catalyst poison. The reaction was found to be reproducible and scalable, and on 20 g, (*Z*)-ethyl chloro-7-hept-3-enonate was isolated in 77% yield.



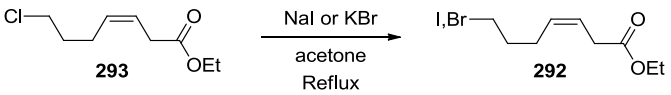
Scheme 115 - Reduction of 294 with nickel boride using nickel chloride

At this stage, direct nitration with silver nitrite on the chloro-derivative was attempted. As expected, the C-Cl bond was not reactive enough to allow the nitration and a Finkelstein reaction was performed to obtain the iodo-derivative.

6.4.1.3 Synthesis of ethyl iodo-7-hept-3-enonate 292

The Finkelstein reaction allows the nucelophilic substitution of chlorides for iodides in organic compounds. Sodium chloride is not soluble in acetone: as it is formed during the reaction, it precipitates out of the solvent. Since, sodium iodide is soluble in acetone the reaction the equilibrium of the reaction is shifted towards completion, according to Le Chatelier principle.

The reaction was attempted in refluxing acetone using NaI and KBr. According to the ^{1}H NMR and mass spectrometry, the reaction with NaI gave full conversion to the corresponding organoiodide, whereas the reaction with KBr did not provide any product.[103] Therefore, the reaction using NaI was scaled up. The reaction was reproducible and scalable (Table 54) and on 3.8 g, ethyl iodo-7-hept-3-enonate **292** was obtained in 95 % crude yield.



Entry	293	Salt	Conversion (by ^{1}H NMR)	Yield (crude)
1	0.1 g	NaI	100 %	Not determined
2	0.1 g	KBr	0 %	-
3	0.6 g	NaI	100 %	90 %
4	1.3 g	NaI	100 %	91 %
5	3.8 g	NaI	100 %	95 %

Table 47 – Optimization towards iodo-alkene 292

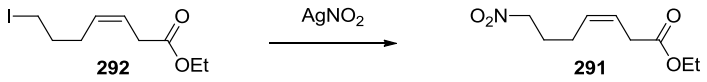
[103] Baughman, T. W.; Sworen, J. C.; Wagener, K. B. *Tetrahedron* **2004**, *60*, 10943.

In order to avoid any decomposition of an unstable compound, the iodo-derivative was used in the next step without further purification.

6.4.1.4 Synthesis of ethyl nitro-7-hept-3-enonate 291

One of the most important methods for the preparation of nitroalkanes is the reaction of alkyl halides with metal nitrites.[104] Various metals have been used: silver (Victor-Meyer reaction), potassium, sodium (Kornblum reaction), *etc*. In most cases, the products are obtained as a mixture for nitroalkane and ester nitrite depending on the ratio of *N*-alkylation *vs O*-alkylation.

The nitro-derivative was obtained by substitution of the primary iodo-compound with silver nitrate (Table 55). The reaction was performed in diethyl ether and in water. In water, the reaction was twelve times faster and gave a comparable or improved yield compared with the reaction with diethyl ether. A longer reaction time, of about 2 days, provided an improved conversion to the desired product.



292 291

Entry	292	Solvent	T (˚C), time	Yield over 2 steps
1	0.1 g	Et_2O	0 ˚C (12h), RT (12h)	30 %
2	0.8 g	Et_2O	0 ˚C (12h), RT (12h)	40 %
3	0.2 g	H_2O	RT, 2h	62 %
4	1.0 g	H_2O	RT, 2h	40 %
5	1.9 g	H_2O	RT, 2h	40 %
6	3.0 g	H_2O	RT, 48h	65 %
7	5.0 g	H_2O	RT, 48h	70 %

Table 48 – Optimization of the nitration

This reaction was easily performed on multigram scale, with yields ranging from 65% to 70%.

6.4.1.5 Synthesis of ethyl [3-(3-nitropropyl)oxiran-2-yl]acetate 289

A *syn*-epoxide was essential to fix the relative stereochemistry of the product in the nitro-Mannich / alkylation / lactamisation step.[105] The opening of the *syn*-epoxide *via* the amine of the nitro-Mannich

[104] (a) Kornblum, N.; Ungnade, H. E. *Org. Synth.* **1963**, *Coll. Vol. 4*, 724. (b) Bidd, I.; Whiting, M. C. *Tetrahedron Lett.* **1984**, *25*, 5949.
[105] Murray, R. W.; Singh, M. *Org. Synth.* **1998**, *9*, 288.

product *via* a SN_2 mechanism would generate the desired *trans* relationship between the proton at the ring junction and the alcohol moiety.

The first reagent which was tried to achieve the *syn*-epoxidation was *m*CPBA. Indeed, *m*CPBA is commonly used to perform such reaction, as it is known to react with a C=C double bond *via* a concerted mechanism to yield the *syn*-epoxide.

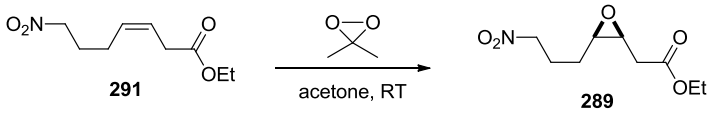
The reaction was done several times, in the presence or in the absence of a neutral buffer (Table 49). Very surprisingly, in all cases, a 1:1 mixture of *syn* and *anti* isomers was obtained. In order to evaluate the influence of the nitro group in this reaction, the chloro-derivative was treated with *m*CPBA under similar conditions. In this case, we obtained the expected result: a mixture 95:5 *syn*/*anti*.

Entry	X	Scale	Conditions	Product	Yield
1	NO_2	100 mg	Buffer pH = 7	*syn*/*anti* 1:1	90 %
2	NO_2	100 mg	-	*syn*/*anti* 1:1	90 %
3	Cl	100 mg	-	*syn*/*anti* 95:5	75 %
4	I	280 mg	-	decomposition	-

Table 49 – Epoxidation with mCPBA

Then, the use of dimethyldioxirane (DMDO), a commonly used reagent for epoxidation of alkenes, was investigated.[106] DMDO can be readily prepared from the reaction of acetone with oxone. The reaction is performed at -15 ˚C, and the product is continuously distilled under reduced pressure. DMDO in acetone is collected in a flask at -78 ˚C. DMDO is a powerful and convenient epoxidising reagent as the only by-product formed during the reaction is acetone. In addition, DMDO reacts rapidly with *Z*-alkenes (7 to 9 times faster than with a *E*-alkene), as it can approach the C=C double bond in a less hindered fashion. The reaction is believed to proceed *via* a *cis-spiro* transition state, *via* a concerted mechanism, to afford exclusively the *cis*-epoxide. The reaction was tested on 50 mg of **291** and the desired *syn*-epoxide **289** was obtained in 65% yield (Table 57). The reaction conditions were found to be reproducible and scalable with up to 87% yield on a 2 g scale (entry 5).

[106] (a) Waldemar, A.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Srivastava, V. P. *Synlett.* **2008**, *4*, 626.



Entry	291	Syn:anti	Yield
1	50 mg	95:5	37 % pure (65 % total)
2	200 mg	95:5	53 %
3	510 mg	95:5	85 %
4	1.2 g	95:5	86 %
5	2.0 g	95:5	87%

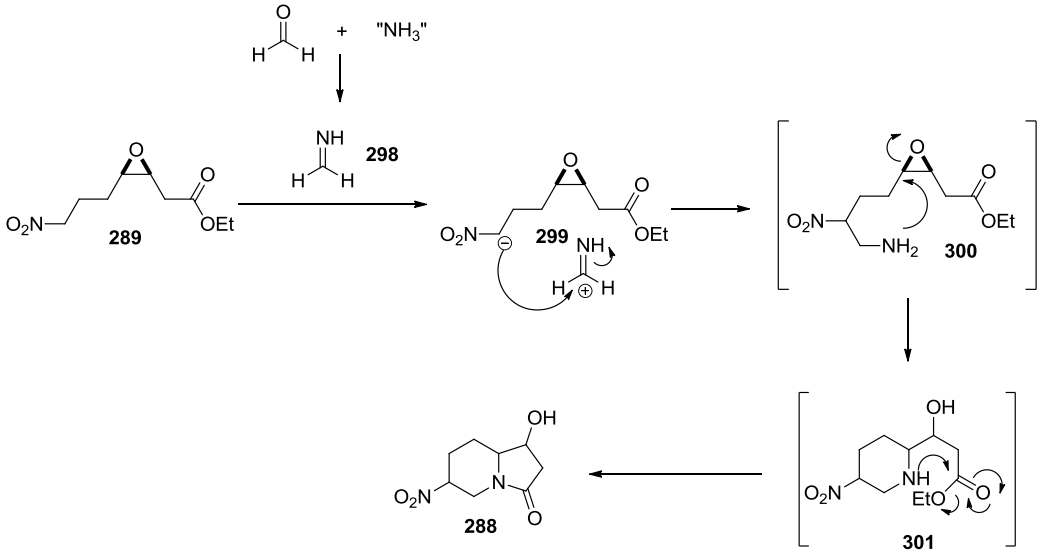
Table 50 – Epoxidation with DMDO

With the key intermediate bearing all the desired functionalities in hand: a terminal nitro group, a terminal ester moiety and a central epoxide, the nitro-Mannich / epoxide opening / lactamisation cascade could be attempted.

6.4.2 The nitro-Mannich / alkylation / lactamisation cascade

6.4.2.1 The plan

The nitro-Mannich / alkylation / lactamisation cascade was designed to be the key step of our total synthesis of slaframine **242**. Ideally, the imine **298** could be formed from the reaction of formaldehyde **9** with a precursor of ammonia (Scheme 116). A reversible nitro-Mannich reaction between this imine formed *in situ* and **289** would give rise to the corresponding intermediate **300**. An intramolecular alkylation of amine moiety onto the epoxide functionality of **300** should form the 6-membered ring (formed preferentially over the 7-membered ring) **301**. Finally and to complete this cascade, an intramolecular lactamisation would lead to the 5,6-bicycle **288**.



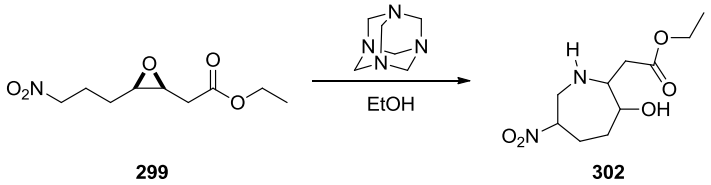
Scheme 116 - The nitro-mannich / alkylation / lactamisation cascade

6.4.2.2 Attempts at the Nitro-Mannich / alkylation / lactamisation cascade

Practically speaking, formaldehyde is available in two forms: as a 30% solution in water, or as the polymer paraformaldehyde which can be “cracked” to the corresponding gaseous monomer upon heating. Both of them were tried in combination with a variety of ammonia equivalents: ammonium acetate, ammonium formate, bis-trimethylsilyl ammonia, etc.

In all cases, the reaction provided a very complex mixture of products. In some cases, the product of a double nitro-Mannich reaction was isolated, due to the high reactivity of formaldehyde, but none of the desired product was observed.

We then decided to use a preformed imine to probe the reactivity. Hexamethylenetetramine is ideally suited for this synthesis as, on heating, it would generate *in situ* the desired imine for this step. Unfortunately, reaction with hexamethylenetetramine at room temperature provided the 7-membered ring **302** shown in Scheme 117 and at reflux it created a complex mixture.

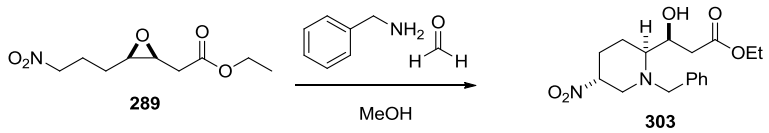


Scheme 117 - The nitro-Mannich / alkylation /lactamisation cascade with hexamethylenetetramine

6.5 End game towards a formal synthesis of slaframine 242[107]

6.5.1 Nitro-Mannich / epoxide opening cascade

Additional work had been conducted to attempt a one-pot nitro-Mannich / epoxide opening / lactamisation cascade, but they all failed. A stepwise approach was considered: first a nitro-Mannich / epoxide opening cascade with a N-protected imine in order to prevent further lactamisation, then removal of the protected group and subsequent cyclisation. Thus benzylamine was reacted with formaldehyde in methanol, followed by the slow addition of epoxide **289**. The reaction was heated at reflux and, pleasingly upon completion a small amount of the desired product **303** (13 % yield) was isolated as a 3:1 mixture of diastereomers (Scheme 118).



Scheme 118 - Nitro-Mannich / alkylation cascade

This result was a very promising even though the undesired side product of a double nitro-Mannich reaction was also isolated. Using an excess of epoxide **289** prevented the formation of the side produtc, and on 200 mg scale in ethanol, **303** was isolated in a very good 68 % yield with a diastereoisomeric ratio of 3:1. The stereochemistry of the major diastereoisomer was determined by nOe experiment.

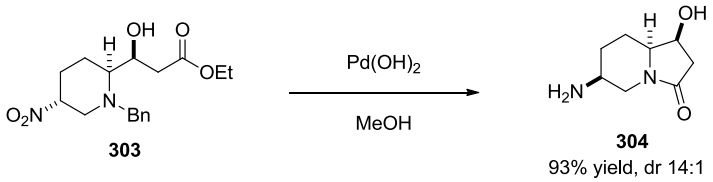
6.5.2 Deprotection and reduction

The *N*-benzyl group is typically cleaved using H_2 with a palladium catalyst. In the present case, the use of a palladium catalyst is particularly interesting since, according to the work by Hoppe et al.,[96] the reduction of the nitro group goes via an oxime intermediate and should allow us to obtain the desired stereochemistry.

As predicted, the nitro group and benzyl protecting group were successfully reduced using $Pd(OH)_2$ in methanol, under an atmosphere of hydrogen. The primary amine formed in situ subsequently

[107] Benjamin Brash, Part II thesis, « Towards the total synthesis of slaframine.

lactamised to afford desired product **304** in an excellent yield (93%) and very good diastereocontrol (14 : 1) (Scheme 119).

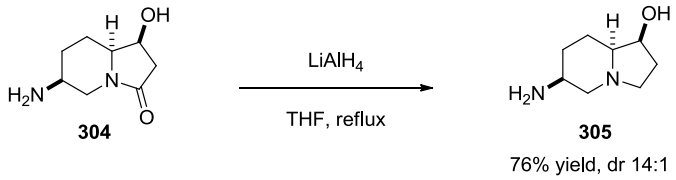


Scheme 119 – Cleavage of the benzyl group and subsequent lactamisation

This was a significant result, since stereoselective access to the 5,6-bicycle had been achieved in an excellent yield of 93%. The stereochemistry of the major diastereoisomer was determined by nOe experiment.

6.5.3 Lactam carbonyl reduction

Reduction of the lactam carbonyl was achieved with $LiAlH_4$. The desired product **305** was isolated in 76% yield and an excellent diastereomeric ratio of 14:1 in favor of the desired diastereoisomer (Scheme 120).

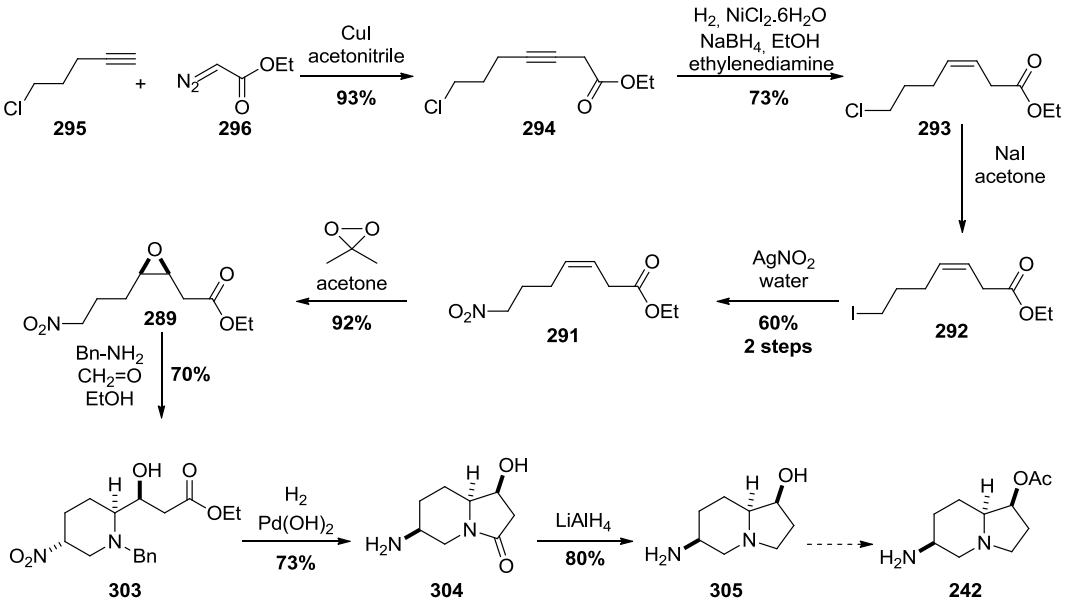


Scheme 120 – Reduction of the lactam of 304

Slaframine 1 is known to be unstable and difficult to isolate and therefore the work was stopped with this efficient formal synthesis of slaframine **242**.

6.6 Conclusion and future plan

A formal synthesis of (±)-slaframine **242** was successfully achieved in a short 8 steps sequence and in excellent overall yield of 15% (Scheme 121).



Scheme 121- Our formal synthesis of racemic slaframine

In the future, an enantioselective epoxidation of **291** under Shi's catalyst system should allow the enantioselective synthesis of (-)-slaframine **242**.

CHAPTER 7

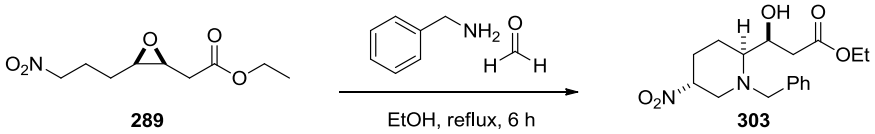
Studies Towards the Development

of

A Nitro-Mannich / Epoxide Opening Cascade Reaction

7.1 Context

The nitro-Mannich / epoxide ring opening cascade reaction developed for the formal synthesis of slaframine **242** (chapter 6) represents a useful tool for the synthesis of pyrrolidine and piperidine heterocycles (Scheme 122).



Scheme 122 - Nitro-Mannich / epoxide ring opening cascade for the synthesis of slaframine 242

A cascade reaction involving the opening of an epoxide was reported by Roush and co-workers in the enantioselective total synthesis of (-)-swainsonine **306** (Figure 20).[108]

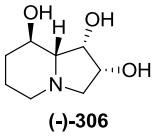
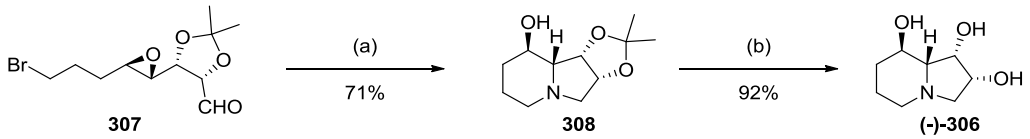


Figure 20 – (-)-Swainsonine 306

As the key step, they constructed the 5,6-core of (-)-swainsonine **306** in one-pot *via* a reductive amination / epoxide ring opening / lactamisation cascade from aldehyde **307** (Scheme 123).



(a) NH_4OAc, 3Å M. S., MeOH, reflux, 6 h; $NaCNBH_3$, RT, 12 h (b) 6N HCl-THF, RT, 12 h

Scheme 123 – Synthesis of (-)-swainsonine 306

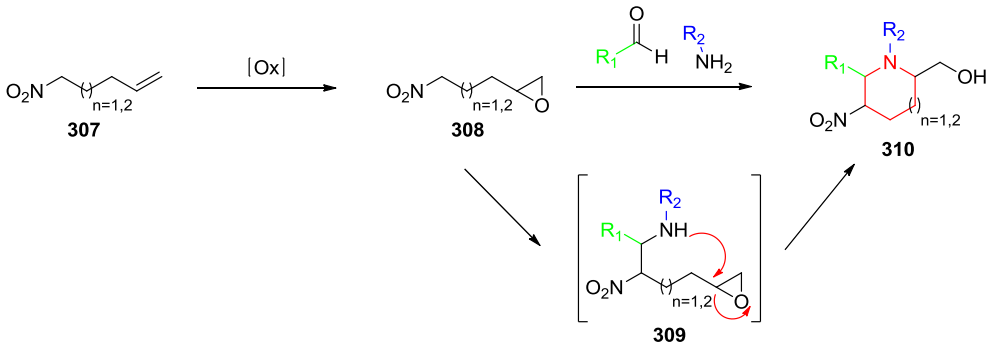
However, to the best of our knowledge, there is no previous example of a nitro-Mannich / epoxide ring opening cascade reaction in the literature and we decided to develop a general method that could be employed routinely to access the corresponding heterocycles.

[108] Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112.

7.2 First approach to develop a general nitro-Mannich / epoxide ring opening cascade

7.2.1 The plan

In order to develop a general method for a nitro-Mannich / epoxide ring opening cascade, a compound bearing a terminal nitro group and an epoxide moiety was required. Nitroalkenes **307a** and **307b** were found to be commercially available and an epoxidation reaction could easily give access to nitro-epoxides **308a** and **308b** (Scheme 124). If successful, the reaction of nitro-epoxides **308** with an aldehyde and an amine could in theory give rise to 6 and 7 membered ring heterocycles **310**.

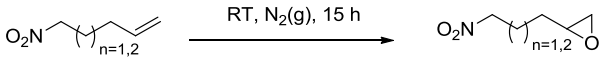


Scheme 124 - First approach to a nitro-Mannich / epoxide ring opening cascade

7.2.2 Synthesis of nitro-epoxides 308

The epoxidation of alkenes has been studied extensively and *m*CPBA is routinely employed to perform such a transformation, giving rise to the *cis* epoxide. Nevertheless, during the synthesis of slaframine **242**, we experienced some difficulties with this reaction which lead to an unexpected 1:1 mixture of *cis* and *trans* epoxide. Dimethyldioxirane (DMDO) was used to overcome the problem and epoxidation to the *cis* product was achieved successfully. In the present case, since the alkene functionality is terminal, the question of the diastereocontrol is not raised. The epoxidation reaction was first tested on 5-nitropent-1-ene **307a** with DMDO and *m*CPBA (Table 51, entries 1 and 2) to compare the efficiency of the oxidants. In both cases, 2-(3-nitropropyl)oxirane **308a** was obtained in excellent yields (> 95%). *m*CPBA was selected to perform this reaction as it is commercially available.

The reaction of **307a** with *m*CPBA was easily scaled up to 900 mg (entry 3) and 2-(4-nitrobutyl)oxirane **308b** was also synthesised in a similar fashion (entry 4).



307
307a n=1
307b n=2

308
308a n=1
308b n=2

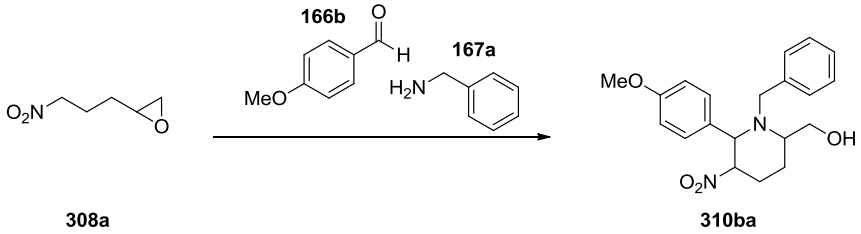
Entry	307	Oxidant	Solvent	Scale	Time	Yield
1	**307a**	DMDO	acetone	50 mg	15h	> 95%
2	**307a**	*m*CPBA	CH_2Cl_2	50 mg	15h	> 95%
3	**307a**	*m*CPBA	CH_2Cl_2	900 mg	15h	> 95%
4	**307b**	*m*CPBA	CH_2Cl_2	150 mg	15h	> 95%

Table 51 – Epoxidation of nitroalkenes 307a and 307b

With epoxides **308a** and **308b** in hand their reactivity towards a nitro-Mannich / epoxide ring opening cascade could then be probed.

7.2.3 Reactivity in the nitro-Mannich / epoxide ring opening cascade

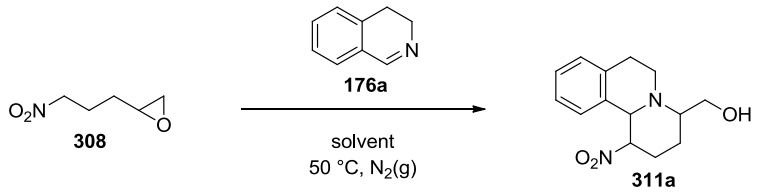
A first reaction was done using similar conditions to those developed in the synthesis of slaframine **242**. In the present case, formaldehyde **9b**, used previously, was changed for *p*-anisaldehyde **166b** to avoid the potential formation of the side product of a double nitro-Mannich reaction. Accordingly, 2-(3-nitropropyl)oxirane **308a** was reacted with *p*-anisaldehyde **166b** and benzylamine **167a** in ethanol at 70 °C (Scheme 125).



308a **310ba**

Scheme 125 – Probing the reactivity of 6 towards a nitro-Mannich / epoxide ring opening cascade

Unfortunately, the reaction generated a complex mixture and gave rise to six different unidentifiable products. The imine system was changed to a preformed cyclic imine to limit the occurrence of side reactions such as the direct intermolecular nucleophilic attack of the amine **167a** on the epoxide moiety of **308a**. 2-(3-Nitropropyl)oxirane **308a** was reacted with 3,4-dihydroisoquinoline **176a** in a variety of solvents at 50 °C and the conversion was monitored by TLC (Table 52).



Entry	Solvent	Conversion to 311a (%)
1	MeOH	-
2	EtOH	-
3	CH_3CN	-
4	CH_2Cl_2	-
5	THF	-
6	Toluene	-
7	Heptane	-

Table 52 – Probing the reactivity with cyclic imine 9a

A selection of solvents, ranging from polar protic to apolar aprotic, was tested (entries 1-7). In all cases, the reaction provided a complex mixture of products. Epoxides are fairly reactive entities and terminal epoxides particularly. Therefore, it was concluded that to tame reactivity a different nitroepoxide substrate bearing an internal epoxide should be synthesised.

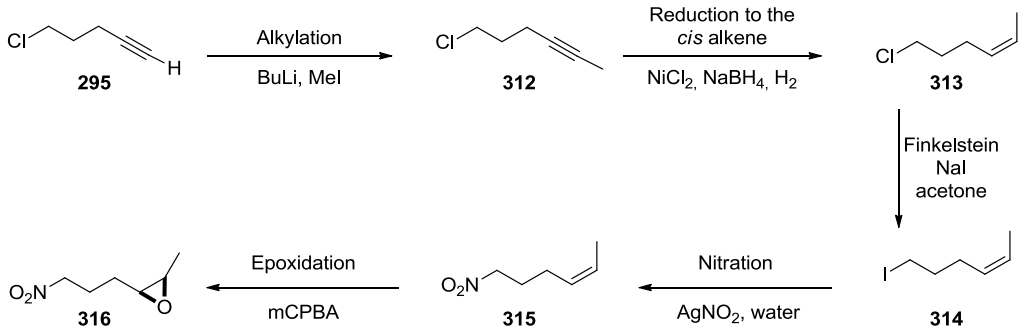
7.3 Second approach to develop a general nitro-Mannich / epoxide ring opening cascade

7.3.1 The plan

Several ways were considered to synthesise a compound bearing a terminal nitro-group and an internal epoxide. First, we envisaged performing a metathesis reaction on 5-nitropent-1-ene **307a** in order to extend the carbon chain and obtain an internal alkene. But even though 5-nitropent-1-ene **307a** is commercial, it is expensive (1 g/£100, Sigma-Aldrich). Also, 4-nitrobut-1-ene, which would allow the synthesis of the corresponding pyrrolidines, is not commercially available. Therefore, it was decided to follow a similar reaction path to the one used in the formal synthesis of slaframine **242** as the chemistry had been previously optimised (Scheme 126). The alkylation of 5-chloropentyne **295** with methyl iodide would give rise to alkyne **312**.[109] A reduction of the alkyne moiety to the

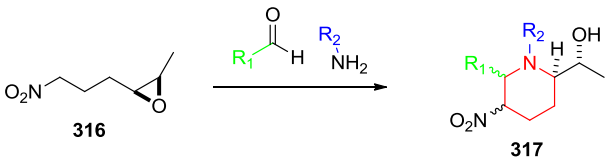
[109] Jakubec, P.; Kyle, A.; Calleja, J.; Dixon, D.J. *Tetrahedron Lett.*. **2011**, *52*, 6094.

corresponding alkene, followed by a Finkelstein reaction and a nitration would allow us to access nitro-alkene **315**. Finally, an epoxidation reaction would enable the synthesis of **316** in 5 steps.



Scheme 126 – Proposed synthesis scheme towards the synthesis of nitro-epoxide 316

If the nitro-epoxide **316** can be successfully prepared we could then probe the nitro-Mannich / epoxide opening cascade reaction to see if it can be used generally to form piperidines like **317** (Scheme 127).

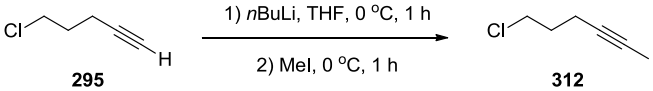


Scheme 127 – Proposed nitro-Mannich / epoxide ring opening cascade for the synthesis of 317

7.3.2 Synthesis of substrate 316

7.3.2.1 Synthesis of 6-chlorohex-2-yne 312

The alkylation of 5-chloropentyne **295** was performed following a literature procedure for a similar chloro-alkyne. 5-Chloropentyne **295** was deprotonated with *n*-BuLi in tetrahydrofuran at 0 ˚C, then alkylated with MeI (Scheme 128).



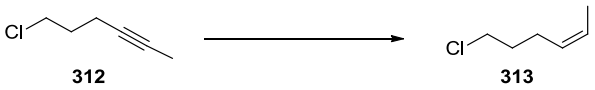
Scheme 128 – Synthesis of 6-chlorohex-2-yne 312

The reaction was performed on 10 g scale to yield 6-chlorohex-2-yne **312** in 90% yield after purification.

7.3.2.2 Synthesis of (*Z*)-6-chlorohex-2-ene 313

The reduction of 6-chlorohex-2-yne **313** to the corresponding *cis* alkene analog **314** was first done using nickel boride in the conditions previously used in the synthesis of slaframine **242** (Table 53, entry 1). Unfortunately, after stirring at room temperature for 3 hours only starting material was recovered. The reaction was repeated and allowed to stir at room temperature overnight (entry 2): a product was isolated. The ^{1}H NMR spectrum revealed signals characteristic of an alkene functionality but no signals characteristic of chloromethyl group; suggesting it had decomposed during the reaction.

Accordingly, various reaction conditions were tested including nickel boride (formed from the reaction of nickel acetate with sodium borohydride, entries 3 and 4), Pd/$CaCO_3$ poisoned by lead in a selection of solvents at room temperature and at 60 °C (entries 5-10), Pd/$CaCO_3$ reduced, in the presence or the absence of quinoline, in a range of solvents, at room temperature and 60 °C (entries 11-20) and finally, Pd/C in the presence or not of quinoline at room temperature and 60 °C (entries 21-23).



312 313

Entry	Catalyst system	Additive	Solvent	Temperature/ Reaction time	Product
1	$NiCl_2.6H_2O$, $NaBH_4$	ethylenediamine	EtOH	RT, 3 h	starter
2	$NiCl_2.6H_2O$, $NaBH_4$	ethylenediamine	EtOH	RT, 18 h	side product
3	$Ni(AcO)_2.6H_2O$, $NaBH_4$	ethylenediamine	EtOH	RT, 6 h	starter
4	$Ni(AcO)_2.6H_2O$, $NaBH_4$	ethylenediamine	EtOH	60 °C, 6 h	starter
5	$Pd/CaCO_3$ poisoned lead	Quinoline	Petrol	RT, 24 h	traces
6	$Pd/CaCO_3$ poisoned lead	Quinoline	Petrol	60 °C, 24 h	traces
7	$Pd/CaCO_3$ poisoned lead	Quinoline	EtOAc	RT, 24 h	traces
8	$Pd/CaCO_3$ poisoned lead	Quinoline	EtOAc	60 °C, 24 h	traces
9	$Pd/CaCO_3$ poisoned lead	Quinoline	EtOH	RT, 24 h	traces
10	$Pd/CaCO_3$ poisoned lead	Quinoline	EtOH	60 °C, 24 h	traces
11	$Pd/CaCO_3$ reduced	Quinoline	Petrol	RT, 24 h	traces
12	$Pd/CaCO_3$ reduced	Quinoline	Petrol	60 °C, 24 h	traces
13	$Pd/CaCO_3$ reduced	Quinoline	EtOAc	RT, 24 h	traces
14	$Pd/CaCO_3$ reduced	Quinoline	EtOAc	60 °C, 24 h	traces
15	$Pd/CaCO_3$ reduced	Quinoline	EtOH	RT, 24 h	traces
16	$Pd/CaCO_3$ reduced	Quinoline	EtOH	60 °C, 24 h	traces
17	$Pd/CaCO_3$ reduced	Quinoline	EtOH	RT, 24 h	traces
18	$Pd/CaCO_3$ reduced	Quinoline	EtOH	60 °C, 24 h	traces
19	$Pd/CaCO_3$ reduced	-	EtOH	RT, 24 h	traces
20	$Pd/CaCO_3$ reduced	-	EtOH	60 °C, 24 h	traces
21	Pd/C	Quinoline	EtOH	RT, 24 h	20%
22	Pd/C	Quinoline	EtOH	60 °C, 24 h	20%
23	Pd/C	-	EtOH	60 °C, 24 h	20%

Table 53 – Screening of reaction conditions for the synthesis of 6-chlorohex-2-ene 313

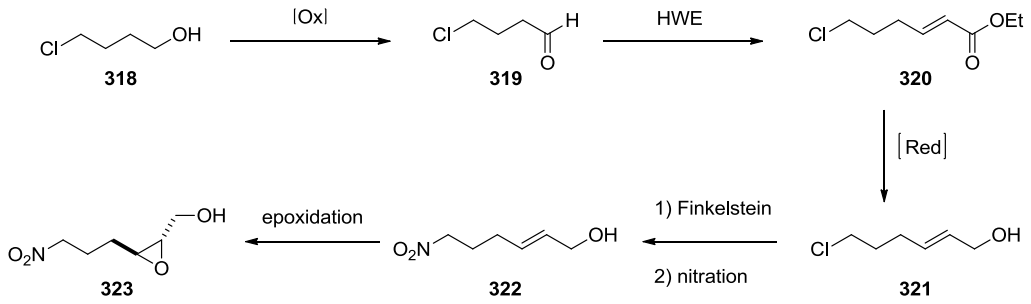
Disappointingly, only traces of products could be observed under all of the conditions tested. Therefore a different approach was considered.

7.4 Third approach

7.4.1 The plan

In order to circumvent the problems created by a catalytic reduction, it was decided to construct the alkene functionality *via* a Horner-Wadsworth-Emmons reaction between 4-chlorobutanal **319** and a stabilised phosphonate carbanion to obtain ethyl (2*E*)-6-chlorohex-2-enoate **320** (Scheme 129). The reduction of the ester moiety of **320** would give rise to the allylic alcohol **321**. Finally, a Finkelstein reaction followed by a nitration and an epoxidation reaction would provide the desired nitro-epoxide **323**. This route presents the strong advantage, compared to the previous ones, that the allylic

alcohol intermediate **322** can be transformed into chiral epoxides *via* a Sharpless epoxidation, therefore providing a possible route towards an enantioselective synthesis of piperidines. A similar reaction scheme starting from 3-chloropropanol would allow access to the pyrrolidinone analogs.



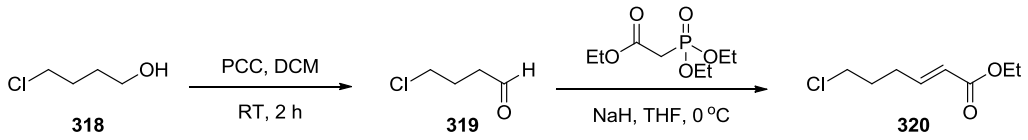
Scheme 129 – Proposed reaction scheme towards the synthesis of nitro-epoxide 323

7.4.2 Synthesis of nitro-epoxide 323 in 5 steps

7.4.2.1 Synthesis of (2*E*)-6-chlorohex-2-enoate 19 in 2 steps from 5-chlorobutanol 318

The synthesis of (2*E*)-6-chlorohex-2-enoate **320** was done in 2 steps (Table 54). First, the oxidation of the primary alcohol 4-chlorobutanol **318** to the corresponding aldehyde **319** was performed using pyridinium chlorochromate (PCC) following a literature procedure.[110] It was initially attempted on 2 g scale and purification was achieved by flash column chromatography; unfortunately, only 12% of 4-chlorobutanal **319** was isolated (entry 1). Accordingly, from then on, the organic solvent was cautiously but rapidly removed under vacuum at low temperature to minimise the loss of product **319** (5-chlorohexanal **319** appeared to be quite volatile) and it was used without further purification in the next step (entries 2 to 5). Then, a Horner-Wasdworth-Emmons reaction between 5-chlorobutanal **319** and the carbanion of triethylphosphonoacetate enabled the formation of (2*E*)-6-chloro-2-emoate **320** in yields ranging from 20% to 46% over the two steps (Table 54).

[110] Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpinska, M. *Synthesis* **2007**, *16*, 2491.



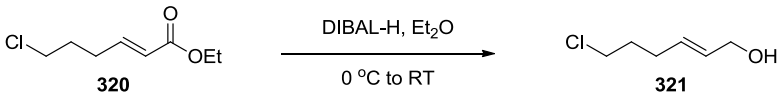
Entry	Scale	Purification	Yield of 319 (%)	Yield of 320 (%)
1	2 g	FCC	12%	30%
2	2 g	Crude	Spot to spot	18%
3	2 g	Crude	Spot to spot	35%
4	5 g	Crude	Spot to spot	46%
5	20 g	Crude	Spot to spot	20%

Table 54 – Synthesis of (2E)-6-chlorohex-2-enoate 320

The yields of isolated **320** were fairly disappointing but, since we had sufficient quantities of **320**, we decided to first test the rest of the route before attempting further optimisations.

7.4.2.2 Synthesis of (2*E*)-6-chlorohex-2-en-1-ol 321

The reduction of the conjugated ester **320** to the allylic alcohol **321** was achieved using DIBAL-H following a literature procedure for the bromide analog of **321** (Table 55).[108] The reaction was first tested on 46 mg and the desired product **321** was isolated in 46% yield (entry 1). The reaction was then scaled up and, on a gram scale, it proceeded smoothly with yields ranging from 85% to 93% (entries 3 and 4).

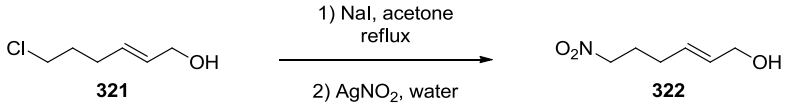


Entry	Scale	Yield of 321 (%)
1	65 mg	46%
2	200 mg	50%
3	1.5 g	93%
4	1.7 g	85%

Table 55 – Synthesis of (2E)-6-chlorohex-2-en-1-ol 321

7.4.2.3 Synthesis of (2*E*)-6-nitrohex-2-en-1-ol 322

In order to synthesise (2*E*)-6-nitrohex-2-en-1-ol **322**, chlorohexenol **321** was first transformed into the corresponding iodohexenol by treatment with sodium iodide *via* a Finkelstein reaction; then it was used without further purification and treated with silver nitrite to yield the desired nitro derivative **322** in 47% yield over the two steps (Table 56).



321 322

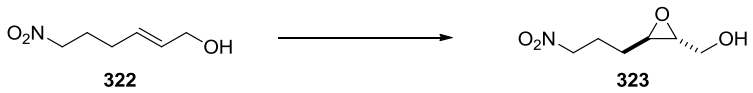
Entry	Scale	Yield of 322 (%)
1	0.2 g	46%
2	1.8 g	47%

Table 56 – Synthesis of (2E)-6-nitrohex-2-en-1-ol 322

The reaction, originally performed on 200 mg scale (entry 1) was easily scaled up to a 1.8 g scale with a similar yield (entry 2).

7.4.2.4 Synthesis of 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitol 323

The epoxidation reaction to the key substrate **323** was tested with DMDO in acetone and *m*CPBA in dichloromethane in parallel to compare the reactivity and the efficiency of both oxidants (Table 57). Since the reaction of (2*E*)-6-nitrohex-2-en-1-ol **322** with these two reagents led to the desired product **323** and provided similar yields (entries 1 and 2), the scale up was performed with commercially available *m*CPBA.



322 323

Entry	Scale	Oxidant	Yield of 323 (%)
1	46 mg	DMDO	83%
2	46 mg	*m*CPBA	85%
3	100 mg	*m*CPBA	86%
4	800 mg	*m*CPBA	70%

Table 57 – Synthesis of 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitol 323

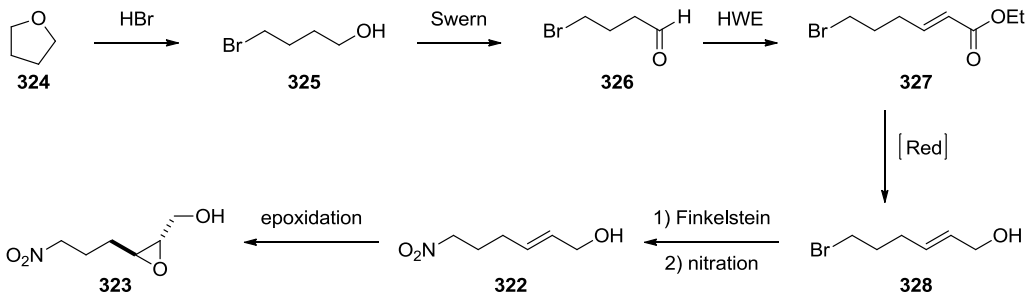
The reaction was scaled up to 100 mg and 800 mg and desired epoxide **323** was isolated in 86% and 70% yield respectively (entries 2 and 3).

7.4.3 Synthesis of nitro-epoxide 323 in 6 steps from a slightly modified route

7.4.3.1 The idea and the route

The synthetic route to nitro-epoxide **323** from 4-chlorobutanol **318** was suffering from the lack of efficiency of the oxidation reaction and the high toxicity of PCC which was used in large excess. Also,

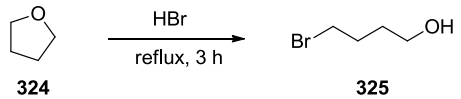
the use of large quantities of 4-chlorobutanol **318** (60£ /50 mL) to afford sufficient quantities of intermediate **323** would become expensive. Accordingly, we investigated a slightly different route (Scheme 130), involving 4-bromobutanol **325**, to tackle those issues. Indeed, 4-bromobutanol can easily be synthesised from the reaction of tetrahydrofuran **324** and HBr on multi-grams scale in a very cost effective fashion. Then, to avoid the use of highly toxic chromium reagents, we decided to perform the oxidation to the corresponding 4-bromobutanal **326** *via* a Swern oxidation.



Scheme 130 – Different approach to the synthesis of nitro-epoxide 323

7.4.3.2 Synthesis of 4-bromobutanol 325

The synthesis of 4-bromobutanol **325** was achieved from the slow addition of HBr to refluxing tetrahydrofuran **324** over 3 hours (Table 58). The excess tetrahydrofuran **324** was then removed under vacuum to provide the desired alcohol **325** which was used without further purification. The reaction was first performed on 40 g of HBr to yield 40% of the desired 4-bromobutanol **325** (entry 1), then it was successfully scaled up to 100 g to yield **325** in 41% and 48% (entries 2 and 3 respectively).



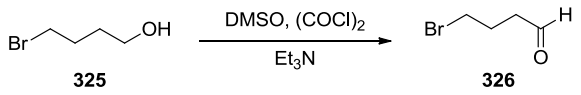
Entry	Scale of HBr	Yield of 325 (%)
1	40 g	40%
2	100 g	41%
3	100 g	48%

Table 58 – Synthesis of 4-bromobutanol 325

With large quantities of 4-bromobutanol **325** in hand, the Swern oxidation could be tested.

7.4.3.3 Synthesis of 4-bromobutanal 326

The oxidation of 4-bromobutanol **325** to 4-bromobutanal **326** was achieved *via* a Swern reaction (Table 59). Unlike the oxidation with PCC, the Swern reaction does not produce any toxic metal waste and it is easy to perform on multi-gram scale. It was first tested on 2 g scale (entry 1) and even though the yield was moderate (25%), it was decided to scale it up, both for practicality and cost efficiency.



325 **326**

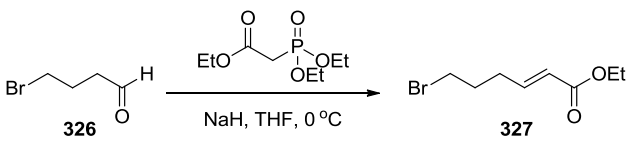
Entry	Scale	Yield of 326 (%)
1	2 g	25 %
2	10 g	Spot to spot
3	10 g	Spot to spot

Table 59 – Synthesis of 4-bromobutanal 326

The reaction was performed twice on 10 g scale (entries 2 and 3) and the desired aldehyde **326** was used without further purification.

7.4.3.4 Synthesis of (*2E*)-6-bromohex-2-enoate 327

(2*E*)-6-Bromohex-2-enoate **327** was synthesised by the same Horner-Wasdworth-Emmons reaction procedure as for (2*E*)-6-chlorohex-2-enoate **320** using triethylphosphonoacetate (Table 60). The reaction was first attempted on 2 g scale of **326**, and **327** was isolated in 30% yield after purification by column chromatography (entry 1). The quality of the aldehyde was thought to be responsible for the disappointing yields. Accordingly, 4-bromobutanal **326** was purified by distillation prior to reaction. Pleasingly, (2*E*)-6-bromohex-2-en-1-ol **327** was obtained in a very good 86% yield (entry 2), confirming our hypothesis. This may also explain the results obtained in section **7-4-2-1** for the synthesis of (2*E*)-6-chlorohex-2-en-1-ol **320**; the reaction was not reproducible and the yields varied from 18% to 46% (Table 54), presumably with varying purity of aldehyde **319**.



326 **327**

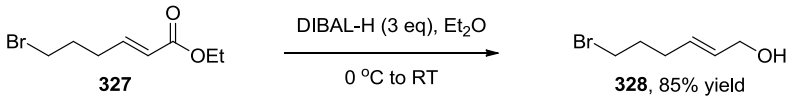
Entry	Scale of 326	Yield of 327 (%)
1	2 g	30 %
2*	900 mg	86%

***In this reaction, **25** was distilled prior to reaction

Table 60 – Synthesis of (2*E*)-6-bromohex-2-enoate 327

7.4.3.5 Synthesis of (2*E*)-6-bromohex-2-en-1-ol 328

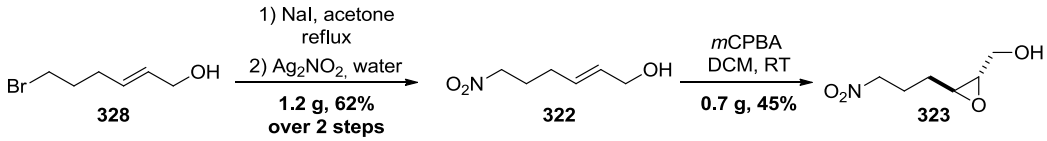
The DIBAL-H reduction of the ester moiety of **327** to the corresponding allylic alcohol **328** was done using the same procedure as the one used for the synthesis of **321**. The reaction was performed on 0.8 g and the desired (2*E*)-6-bromohex-2-en-1-ol **328** was isolated in 85% yield (Scheme 131).



Scheme 131 – DIBAL-H reduction of 327

7.4.3.6 Synthesis of 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitol 323

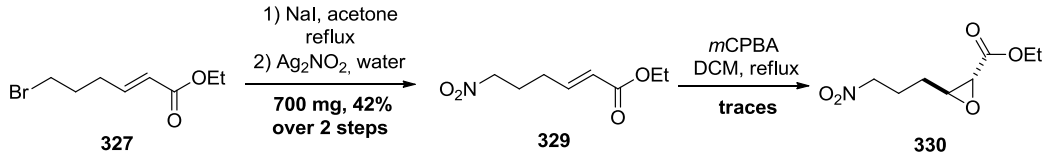
Nitro-epoxide **323** was obtained in an additional three steps, in an identical fashion to the one previously performed on the chloride analog **321**. (2*E*)-6-Bromohex-2-en-1-ol **328** was converted to (2*E*)-6-nitrohex-2-en-1-ol **322** *via* a Finkelstein reaction followed by a nitration with silver nitrite in 62% yield over the two steps (Scheme 132). Finally an epoxidation reaction with *m*CPBA afforded the desired nitro-epoxide **323** in 45% yield.



Scheme 132 – Synthesis of nitro-epoxide 323 in 28% yield over 3 steps

7.4.4 Synthesis of ethyl 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitoate 330

From (2*E*)-6-bromohex-2-en-1-ol **327** it was also decided to synthesise ethyl 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitoate **330** to compare its reactivity with the alcohol analog **323**. This was attempted in 3 steps *via* a Finkelstein reaction, a nitration and an epoxidation reaction (Scheme 133).



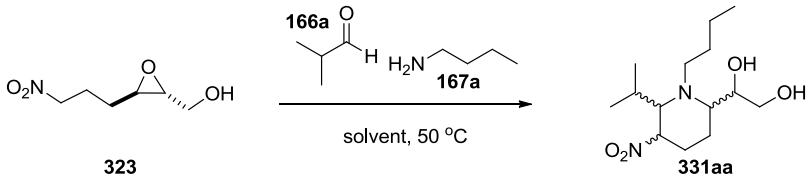
Scheme 133 – Synthesis of ethyl 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitoate 330

Nitroester **329** was successfully synthesised in 42% yield over 2 steps. However, the epoxidation reaction proved to be difficult and only provided traces of the desired product **330** preventing us from testing the nitro-Mannich / epoxide ring opening cascade on this substrate.

7.4.5 Nitro-Mannich / epoxide ring opening cascade with 323

7.4.5.1 Attempts at a one-pot three component cascade

With the key epoxide **323** in hand we decided to probe the reactivity towards a three component nitro-Mannich / epoxide ring opening cascade with an acyclic imine formed *in situ*. Accordingly, epoxide **323** was reacted with isobutyraldehyde **166a** and butylamine **167a** in a variety of solvents at 50 °C (Table 61).



Entry	Solvent	Conversion to 331aa (%)
1	Water	-
2	MeOH	traces
3	EtOH	traces
4	EtOAc	-
5	Et_2O	-
6	THF	-
7	Acetonitrile	-
8	Chloroform	-
9	Toluene	-
10	Hexane	-

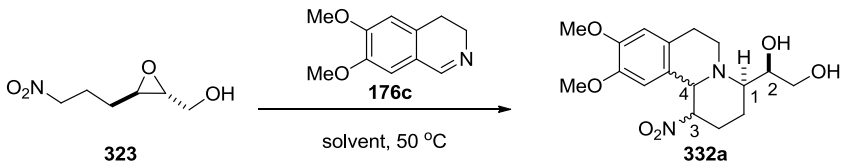
Table 61 – Nitro-Mannich / epoxide ring opening cascade on 323 with acyclic imine formed *in situ*

Encouragingly, in polar protic solvents, such as methanol and ethanol (entries 2 and 3), the ^{1}H NMR spectrum presented interesting signals possibly characteristic of the product **30**. Unfortunately, we were unable to isolate any product and it was decided to attempt the reaction with preformed cyclic imines to limit side reactions.

7.4.5.2 Attempts at the cascade with preformed cyclic imines

1-4-5-2-1- Reaction with 6,7-dimethoxy-3, 4-dihydroisoquinoline 176c

We tried the reaction with 6,7-dimethoxy-3,4-dihydroisoquinoline **176c** in MeOH, tetrahydrofuran and toluene (Table 62).



Entry	Solvent	Conversion to 332a (%)
1	MeOH	55%
2	THF	traces
3	Toluene	-

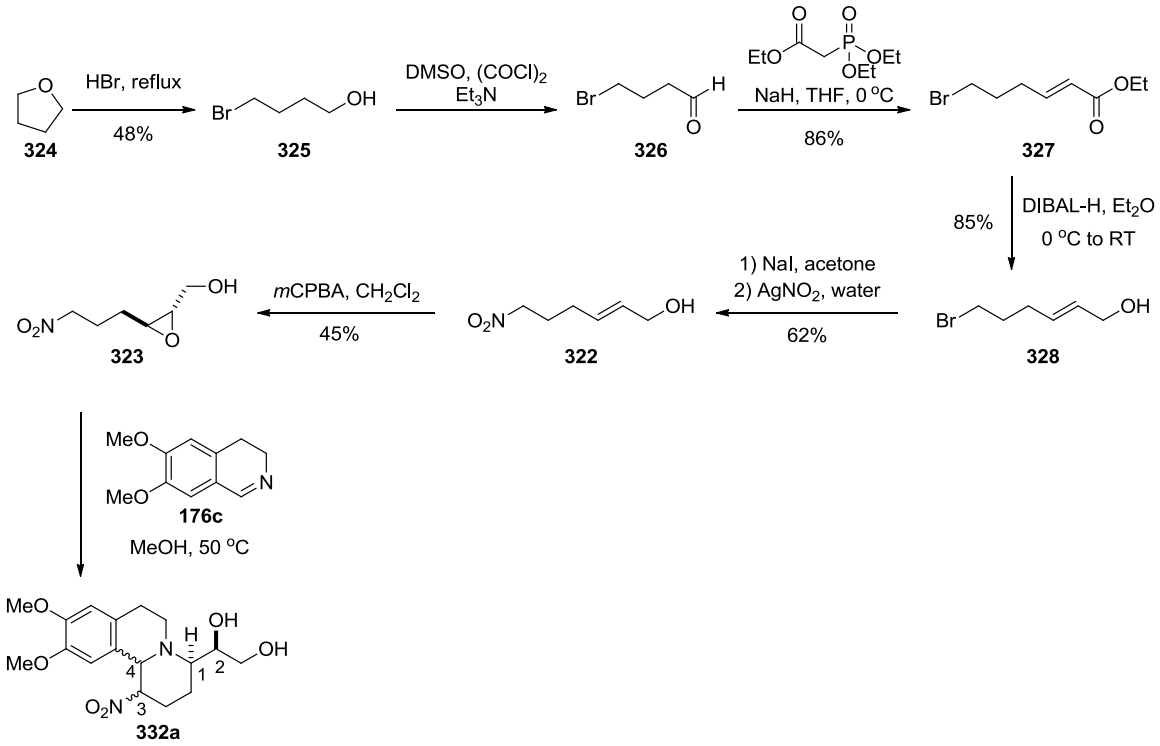
Table 62 – Nitro-Mannich /epoxide ring opening cascade on 332a

In toluene, no reaction was observed and in tetrahydrofuran only traces of a new product was witnessed. Pleasingly in MeOH we were able to isolate a new spot by flash column chromatography in 55% yield (on 25 mg scale). It was fully characterised and pleasingly, it was found to be a 1:1 mixture of two inseparable diastereoisomers of **332**. Piperidine **332** possesses four stereocenters and therefore theoretically 8 diastereoisomers could be formed; however since the stereochemistry of the *trans* epoxide of **323** was fixed, the stereochemistry of the stereocenters 1 and 2 were fixed as well, and accordingly only 4 out of the 8 diastereoisomers were accessible in the reaction. However, we only isolated 2 diastereoisimers which suggests a selective nitro-Mannich reaction (probably in favor of the trans isomer). This very encouraging result was obtained two weeks before the end of my DPhil and I chose to suspend this project on this positive note.

7.5 Conclusion

Several routes and approaches had to be considered and attempted in order to construct a substrate that would allow us to probe a new methodology of a nitro-Mannich / epoxide ring opening cascade. 4,5-Anhydro-1,2,3-trideoxy-1-nitrohexitol **323** was synthesised in 6 steps from tetrahydrofuran in 2% overall yield. Fortunately, the low yielding steps are the two first ones which consist of two reactions easy to perform on multi-grams scale with cheap reagents. After several trials, we successfully

isolated the products of a nitro-Mannich / epoxide ring opening cascade, leading the way to the development of a new methodology (Scheme 134).



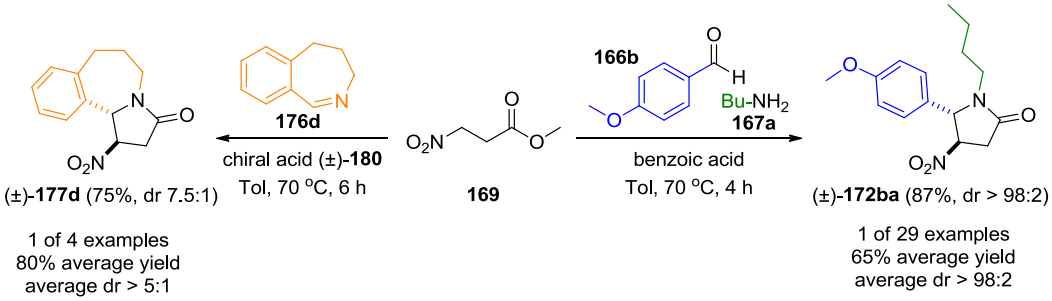
Scheme 134 – Summary

Conclusion

Pyrrolidinone and pyrrolidine heterocycles are very common motifs in both natural products and biologically active compounds. However and beside the large amount of reports in the field, to this date, there was no methodology which allowed the general and straightforward synthesis of these 5-membered rings

In this thesis, through the work undertaken towards a nitro-Mannich / lactamisation cascade of methyl nitropropanoate, we developed the first general methodology for the synthesis of pyrrolidinones with a wide range of substitution patterns.

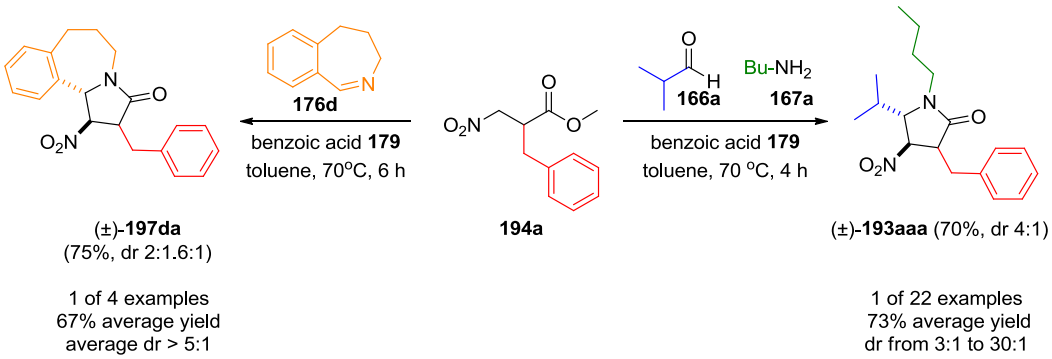
In chapter 1, we described the direct diastereoselective synthesis of *trans* 1,5-disubstituted-4-nitropyrrolidinones **172** *via* a nitro-Mannich / lactamisation cascade between methyl 3-nitropropanoate **169** and an acyclic imine formed *in situ* from the reaction of an aldehyde **166** with an amine **167**. The reaction was easy to perform, very broad in scope and tolerated a wide variety of functional group (halides, esters, alcohols, etc): 28 examples were synthesised with a very good average yield of 72%. Moereover, the method was extended to the reaction with preformed cyclic imines **176** to access fused tricyclic pyrrolidinones **177** in excellent yields (80% in average) and good diastereocontrol (from 4:1 to 14:1) (Scheme 135).



Scheme 135 – Diastereoselective synthesis of monocyclic and fused tricyclic pyrrolidinones 172 and 177

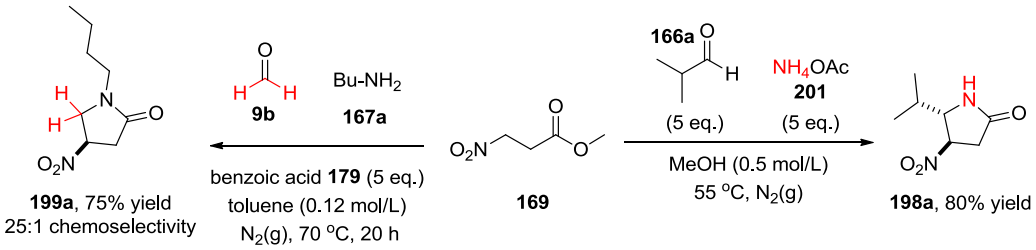
In chapter 2, an efficient diastereoselective nitro-Mannich / lactamisation reaction cascade of methyl 2-alkyl 3-nitropropanoate **194** with imines generated *in situ* was developed (Scheme 136). This versatile extension of the work reported in the previous chapter allowed direct, diastereoselective preparation of 1,3,5-trisubstituted 4-nitropyrrolidin-2-one derivatives **193**. The diastereocontrol was found not to be affected by the reaction parameters (temperature, dilution, stoichiometry and nature of the acid) and to remain constant over time. However, further studies revealed that the diastereoselectivity increased strongly with the steric bulk on the subsituents. The methodology has

also been extended to the reaction with cyclic imines **176** to give rise to fused tricyclic pyrrolidinones **197** in good yields but poor diastereoselectivities.



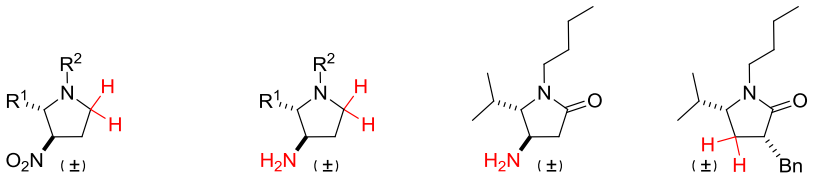
Scheme 136 – **Diastereoselective synthesis of monocyclic and fused tricyclic pyrrolidinones 193 and 197**

In chapter 3, the nitro-Mannich / lactamisation cascade of **169** was developed further to allow the rapid synthesis of 5-isopropyl-4-nitropyrrolidin-2-one **198a** from reaction with ammonium acetate **201** and 1-butyl-4-nitropyrrolidin-2-one **199a** from reaction with formaldehyde **9b** (37% solution in water) (Scheme 137). This advancement is particularly interesting as it strongly increases the scope of the pyrrolidinone synthesis.



Scheme 137 – Further extension of the nitro-Mannich / lactamisation cascade

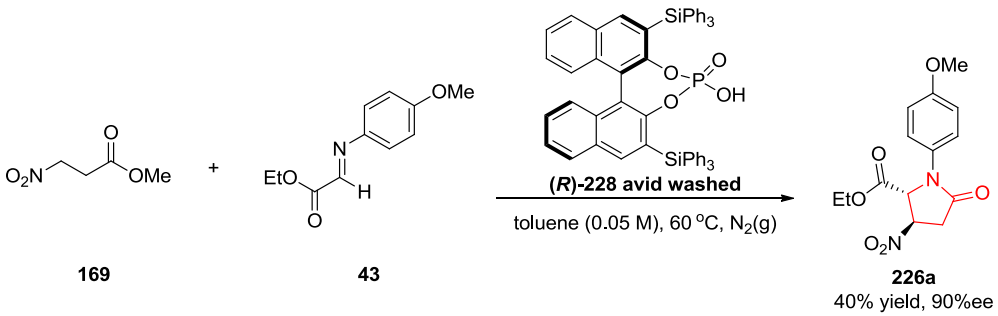
In addition, the synthetic utility of the nitro-pyrrolidinones formed was exemplified through various functional group modifications. The selective reduction of the lactam carbonyl was performed in the presence of the nitro group, the reduction of the nitro group to the corresponding amine was achieved successfully in the presence or absence of carbonyl group and the nitro group was successfully removed under radical conditions to form (Scheme 138).



206, 31% average yield **207**, 73% average yield **208**, 80% yield **209**, 90% yield

Scheme 138 – Various functional group modifications

In chapter 4, an enantioselective nitro-Mannich / lactamisation cascade for the synthesis of pyrrolidinone was successfully discovered and partially developed (Scheme 138). The reaction with imines bearing electron deficient substituents provided the corresponding heterocycles in excellent enantiomeric excess (80% in average) and moderate chemical yield (40% average). Unfortunately, so far, the reaction is limited in scope and in lots of cases the results were not reproducible. In addition, we demonstrated that the nature of the catalyst (acid form *vs* salt) was probably responsible for those limitations and further work is required on this reaction to improve the chemical yield and the scope.

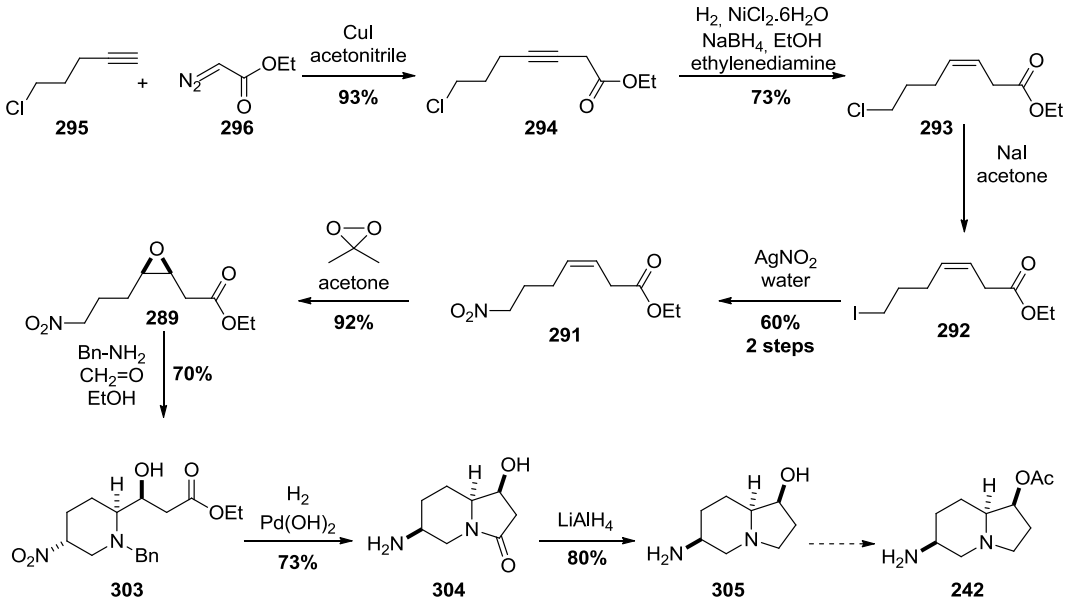


169 **43** **(*R*)-228 avid washed** toluene (0.05 M), 60 °C, N_2(g) **226a** 40% yield, 90%ee

Scheme 139 – Enantioselective nitro-Mannich / lactamisation cascade

In chapter 5, various studies were undertaken in order to try and understand the mechanism of the nitro-Mannich / lactamisation cascade. It was found that aldehydes **24** could be sensitive to the presence of oxygen in the solvent toluene as they could be converted to the corresponding carboxylic acid *via* a radical mechanism. It was also concluded that it is difficult to determine with certainty if the reaction was under thermodynamic or kinetic control but we believe that the diastereocontrol is likely to originate during the rate determining lactamization step of this reaction cascade. Finally, the lower degree of diastereocontrol obtained in the reaction with preformed cyclic imine is probably due to the strain generated by the fused tricyclic core of the pyrrolidinone product.

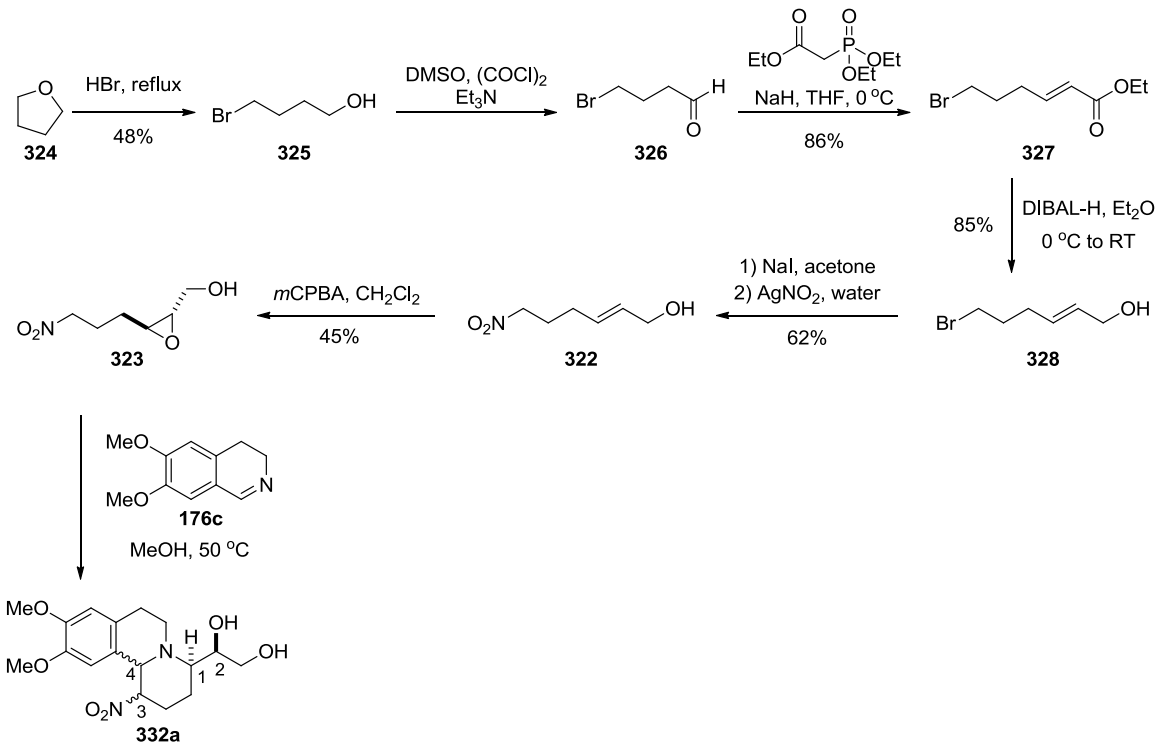
A formal synthesis of (±)-slaframine **242** was successfully achieved in a short 8 steps sequence and in excellent overall yield of 15% (Scheme 140).



Scheme 140 – Formal synthesis of slaframine 242

In the future, an enantioselective epoxidation of **291** under Shi's catalyst system should allow the enantioselective synthesis of (-)-slaframine **1**.

Several routes and approaches had to be considered and attempted in order to construct a substrate that would allow us to probe a new methodology of a nitro-Mannich / epoxide ring opening cascade. 4,5-Anhydro-1,2,3-trideoxy-1-nitrohexitol **22** was synthesised in 6 steps from tetrahydrofuran in 2% overall yield. Fortunately, the low yielding steps are the two first ones which consist of two reactions easy to perform on multi-grams scale with cheap reagents. After several trials, we successfully isolated the products of a nitro-Mannich / epoxide ring opening cascade, leading the way to the development of a new methodology (Scheme 141).



Scheme 141 – Towards a new methodology for a nitro-Mannich / epoxide opening cascade reaction

Appendix A

Supporting Informations

A.0 General experimental

All reactions were performed in degassed but not anhydrous solvent unless otherwise stated and under a nitrogen atmosphere. For reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C and purged with nitrogen.

Solvents and reagents

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Petroleum ether refers to distilled light petroleum of fraction (40 °C – 60 °C). Aldehydes were freshly distilled before undergoing reaction. Reagents used were obtained from commercial suppliers and used without further purification. Dry tetrahydrofuran refers to freshly distilled THF over sodium and benzophenone.

Chromatography

Column chromatography was carried out using VWR Kieselgel 60 silica gel (60-63 μm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F_{254} fluorescent treated silica which were visualised under UV light (250 nm) or by staining with aqueous basic potassium permanganate solutions.

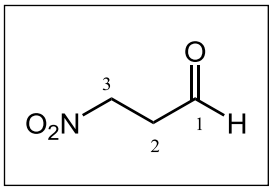
Spectroscopy

All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 500 MHz and are quoted in ppm. Unless otherwise stated all experiments were carried out using $CDCl_3$ as solvent. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: ppm (multiplicity, number of protons, coupling constants, assignment and J/Hz (where appropriate)). Two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. Low resolution mass spectrometry (EI) was recorded on a Waters LCT

Premiers XE Micromass mass spectrometer. High resolution mass spectra (accurate mass) were recorded on a Bruker daltonios MicroTOF mass spectrometer. Infrared spectra were recorded on a Bruker tensor 27 FT-IR spectrometer from a thin film deposited onto a sodium chloride plate or diamante ATR module. Only selected maximum absorbances are reported. ("s" = singlet, "br s" = broad singlet, "d" = doublet, "br d" = broad doublet, "t" = triplet, "q" = quartet, "m" = multiplet, "quint" = quintet, "sext" = sextuplet, "sept" = septuplet, "septd" = septuplet of doublet, "dd = doublet of doublet, "t" = apparent triplet, "dt" = apparent doublet of triplet, "td" = triplet of doublet, "ddd" = apparent doublet of doublet of doublet, "dqd" = doublet of quadruplet of doublet, "dquint" = doublet of quintet

A.1 Experimental- Chapter 1

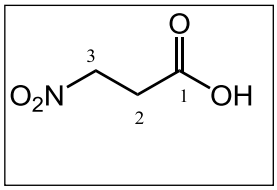
A.1.1. 3-Nitropropanal 174



A 500 mL, 3-necked flask, equipped with a magnetic stirrer bar and nitrogen flow, was charged with water (44 mL), tetrahydrofuran (72 mL) and sodium nitrite (16.0 g, 0.23 mol, 1.3 eq). This was cooled to 0 °C and, with stirring, acrolein **173** (11.9 mL, 0.18 mol, 1.1 eq) was slowly added *via* a syringe, followed by the dropwsise addition of acetic acid (11.9, 0.19 mol g, 1.1 eq) over 30 minutes. The mixture was allowed to stir at 0 °C for three hours behind a blastshield. Then, ethyl acetate (90 mL) was added along with saturated aqueous sodium bicarbonate (40 mL) and the layers were separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed three times with brine, dried over Na_2SO_4 and ethyl acetate was removed under vacuum while maintining the water bath of the rotary evaporator below 20 °C. The residual acetic acid was removed by azeotropic distillation in toluene to give 13.3 g (72 % yield) of 3-nitropropanal **174** as a brown oil. The crude material was used without further purification in the next step.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 3.18 (t, 2H, H-2, *J* 6.0 Hz), 4.68 (t, 2H, H-3, *J* 6.0 Hz), 9.81 (s, 1H, H-1). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 39.5 (C-2), 67.6 (C-3), 196.5 (C-1).

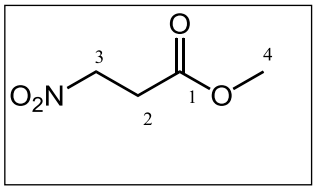
A.1.2. 3-Nitropropanoic acid 175



A 500 mL, 3-necked flask equipped with a magnetic stirrer bar and a thermometer, was charged with 3-nitropropanal **174** (13.0 g, 0.13 mol, 1.0 eq), acetonitrile (100 mL), a solution of sodium dihydrogen phosphate NaH_2PO_4 (3.0 g, 0.02 mol, 0.2 eq) in water (35 mL) and hydrogen peroxide (9.8 mL, 0.11 mol, 0.8 eq). The mixture was cooled in a water bath and a solution of sodium chlorite $NaClO_2$ (80% purity, 15.7 g) in water (130 mL) was added dropwise over 2 hours in order to maintain the temperature below 25 °C. The reaction was monitored by TLC (1:1 petroleum ether / diethyl ether) and by observing the gas formation. Once the reaction was finished, Na_3SO_3 (1 g) was added to destroy the unreacted HOCl and hydrogen peroxide. Water (100 mL) was added, then the product was extracted three times with ethyl acetate. The water layer was saturated with sodium chloride and reextracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and ethyl acetate was removed under vacuum to give 13 g (95 % yield) of 3-nitropropanoic acid **175** as a white solid after trituration in chloroform.

^{1}H NMR (MeOD, 500 MHz) δ_H 2.97 (t, 2H, H-2, *J* 6.0 Hz), 4.70 (t, 2H, H-3, *J* 6.0 Hz). **^{13}C NMR** (MeOD, 125 MHz) δ_C 31.7 (C-2), 71.0 (C-3), 173.4 (C-1).

A.1.3. Methyl 3-nitropropanoate 169

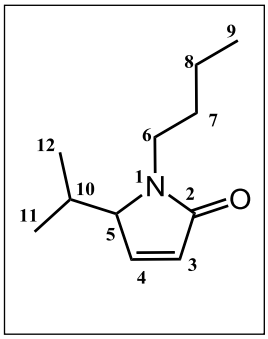


A 500 mL, one-necked flask equipped with magnetic stirrer bar and condenser containing 3Å molecular sieves, was charged with 3-nitropropanoic acid **175** (10 g, 0.08 mol, 1 eq), methanol (200 mL) and sulphuric acid (2 mL). The mixture was refluxed for 4 hours. Methanol was evaporated to give a brown residue which was taken up in dichloromethane and washed three times with water. The

combined water layers were extracted once with dichloromethane. The combined organic layers were dried over Na_2SO_4 and dichloromethane was removed under vacuum. The crude was purified by flash column chromatography (petroleum ether / diethyl ether 2:1) to give 6.0 g (79 % yield) of methyl 3-nitropropanoate **169** as a light yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.98 (t, 2H, H-2, *J* 6.0 Hz), 3.74 (s, 3H, H-4), 4.65 (t, 2H, H-3, *J* 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 30.8 (C-2), 52.4 (C-4), 69.6 (C-3), 169.9 (C-1).

A.1.4. 1-Butyl-5-isopropyl-1,5-dihydro-2*H*-pyrrol-2-one 178



178 was obtained as a side product in the synthesis of **172aa**. It was purified by flash column chromatography (gradient from 10:1 to 2:1 petroleum ether / ethyl acetate) and it was obtained as a light yellow oil (R_f = 0.50 ethyl acetate / petroleum ether 1:1).

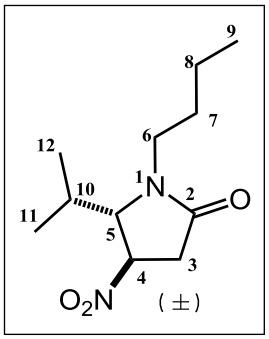
IR (cm^{-1}) ν_{max} 1683 (C=O). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.41 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.71 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 0.88 (t, 3H, H-9, *J* 7.0 Hz), 1.15-1.26 (m, 2H, H-8), 1.28-1.40 (m, 2H, H-7), 1.68-1.81 (m, 1H, H-10), 2.71 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 5.5 Hz), 3.52-3.56 (m, 1H, H-5), 3.79 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 6.03 (dd, 1H, H-3, *J* 6.0 Hz, *J* 1.5 Hz), 6.31 (dd, 1H, H-4, *J* 6.0 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.9 (C-9), 14.7 (C-11 and 12), 19.0 (C-8), 27.8 (C-10), 31.0 (C-7), 39.2 (C-6), 66.6 (C-5), 129.1 (C-3), 143.4 (C-4), 170.5 (C-2). ***m/z*** (ES+) 204 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{19}NONa^+$) requires ***m/z*** 204.1359, found ***m/z*** 204.1361.

A.1.5. General procedure A for the synthesis of pyrrolidin-2-one 172

A 5 mL one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl-3-nitropropanoate **169** (100 mg, 0.75 mmol, 1.0 eq), benzoic acid **179** (138 mg, 1.13 mmol, 1.5 eq) and toluene (2 mL). The reaction mixture was pumped/filled three times with N_2 , then the amine **167** (1.13 mmol, 1.5 eq) and the aldehyde **166** (1.13 mmol, 1.5 eq) were added *via* a

microsyringe. The reaction was stirred at 70 °C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate (typically from 4 to 10 hours). The reaction was monitored by TLC and upon completion, the crude mixture was concentrated under vacuum, the residue was taken up in dichloromethane, washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and purified by flash column chromatography.

A.1.5.1. 1-Butyl-5-isopropyl-4-nitropyrrolidin-2-one 172aa



Prepared according to the general procedure **A**.

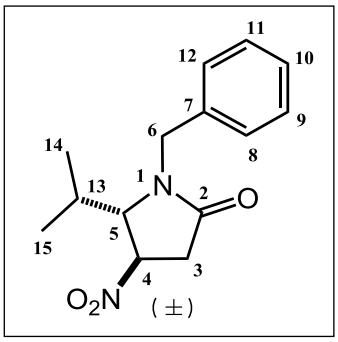
172aa (123 mg, 72%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 10:1 to 2:1 petroleum ether / ethyl acetate) as a light yellow oil (R_f = 0.44 ethyl acetate / petroleum ether 1:1).

IR (cm^{-1}) ν_{max} 1697 (C=O), 1557 (NO_2), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.79 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.93 (t, 3H, H-9, *J* 7.5 Hz), 1.11 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 1.24-1.39 (m, 2H, H-8), 1.42-1.60 (m, 2H, H-7), 2.20 (septd, 1H, H-10, *J* 7.0 Hz, *J* 3.5 Hz), 2.80-2.87 (m, 2H, H-3 and H-6), 3.04 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.76 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.97 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0 Hz), 4.84 (dt, 1H, H-4, *J* 9.0 Hz, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 14.9 (C-11 or 12), 18.2 (C-12 or 11), 19.9 (C-8), 28.2 (C-10), 28.8 (C-7), 35.9 (C-3), 40.2 (C-6), 67.4 (C-5), 78.5 (C-4), 169.8 (C-2). ***m/z*** (ES-) 227 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{20}N_2O_3Na^+$) requires ***m/z*** 251.1366, found ***m/z*** 251.1365.

A.1.5.2. 1-Benzyl-5-isopropyl-4-nitropyrrolidin-2-one 172ab

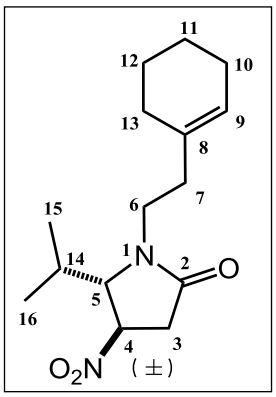
Prepared according to the general procedure **A**.

172ab (149 mg, 76%, single diastereomer) was obtained after purification by flash column chromatography (diethyl ether) as a light yellow amorphous solid (R_f = 0.17 in petroleum / diethyl ether 2:5).



mp 102-105 °C. **IR** (cm^{-1}) ν_{max} 1699 (C=O), 1556 (NO_2), 1496 (aromatic C=C) 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-14 or H-15, *J* 7.0 Hz), 1.01 (d, 3H, H-15 or H-14, *J* 7.0 Hz), 2.17 (septd, 1H, H-13, *J* 7.0 Hz, *J* 3.5 Hz), 2.89 (ddd, 1H, H-3, *J* 18.5 Hz, *J* 9.0 Hz, *J* 1.0 Hz), 3.14 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.73 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0 Hz), 3.90 (d, 1H, H-6, *J* 15.0 Hz), 4.85 (dt, 1H, H-4, *J* 9.0 Hz, *J* 2.0 Hz), 5.14 (d, 1H, H-6', *J* 15.0 Hz), 7.20-7.25 (m, 2H, H_{Ar}), 7.27-7.37 (m, 3H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.8 (C-14 or C-15), 18.0 (C-15 or C-14), 27.8 (C-13), 35.8 (C-3), 44.4 (C-6), 67.0 (C-5), 78.3 (C-4), 127.9 (2x C_{Ar}-H), 128.0 (C_{Ar}-H), 128.9 (2x C_{Ar}-H), 134.8 (C-7), 170.1 (C-2). ***m/z*** (ES+) 285 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}N_2O_3Na^+$) requires ***m/z*** 285.1210, found ***m/z*** 285.1211.

A.1.5.3. 1-[2-(Cyclohex-1-en-1-yl)ethyl]-5-isopropyl-4-nitropyrrolidin-2-one 172ac

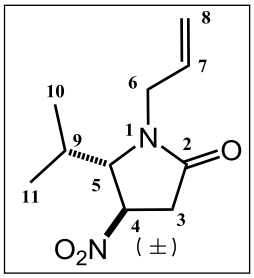


Prepared according to the general procedure **A**.

172ac (161 mg, 76%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 2:1 petroleum ether / diethyl ether to pure diethyl ether) as an orange oil (R_f = 0.10 in petroleum ether / diethyl ether 1:1).

IR (cm^{-1}) ν_{max} 1697 (C=O), 1556 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-15 or H-16, *J* 7.0 Hz), 1.11 (d, 3H, H-16 or H-15, *J* 7.0 Hz), 1.48-1.54 (m, 2H, H-11), 1.54-1.65 (m, 2H, H-12), 1.84-2.04 (m, 4H, H-10 and H-13), 2.07-2.15 (m, 1H, H-7), 2.16-2.24 (m, 2H, H-7' and H-14), 2.76 (ddd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz, *J* 1.0 Hz), 2.85 (dt, 1H, H-6, *J* 14.0 Hz, *J* 6.5 Hz), 3.09 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.91 (dt, 1H, H-6', *J* 14.0 Hz, *J* 7.5 Hz), 4.01 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0 Hz), 4.78 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.0 Hz), 5.39 (br s, 1H, H-9). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 15.0 (C-15 or 16), 18.2 (C-16 or 15), 22.2 (C-11), 22.7 (C-12), 25.2 (C-10), 27.7 (C-13), 28.1 (C-14), 35.3 (C-7 and C-3), 38.1 (C-6), 67.4 (C-5), 78.4 (C-4), 124.2 (C-9), 133.7 (C-8), 169.7 (C-2). ***m/z*** (ES-) 279 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{25}N_2O_3^+$) requires ***m/z*** 281.1860, found ***m/z*** 281.1872.

A.1.5.4. 1-Allyl-5-isopropyl-4-nitropyrrolidin-2-one 172ad

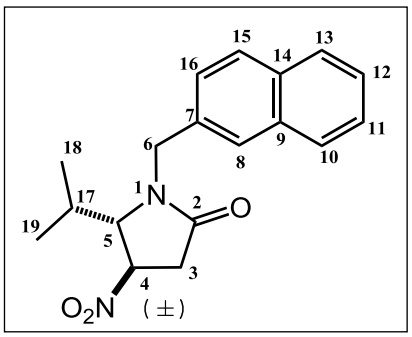


Prepared according to the general procedure **A**.

172ad (110 mg, 70%, single diastereomer) was obtained after purification by flash column chromatography (diethyl ether) as a yellow oil (R_f = 0.20 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1701 (C=O), 1557 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.79 (d, 3H, H-10 or H-11, *J* 7.0 Hz), 1.08 (d, 3H, H-11 or H-10, *J* 7.0 Hz), 2.18 (septd, 1H, H-9, *J* 7.0 Hz, *J* 4.0 Hz), 2.83 (ddd, 1H, H-3, *J* 18.5 Hz, *J* 9.0 Hz, *J* 1.0 Hz), 3.06 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.44 (ddd, 1H, H-6, *J* 15.5 Hz, *J* 7.5 Hz, *J* 1.0 Hz), 3.96 (dd, 1H, H-5, *J* 4.0 Hz, *J* 2.0 Hz), 4.44 (ddt, 1H, H-6', *J* 15.5 Hz, *J* 5.0 Hz, *J* 2.0 Hz), 4.85 (dt, 1H, H-4, *J* 9.0 Hz, *J* 2.0 Hz), 5.20-5.27 (m, 2H, H-8), 5.70 (dddd, 1H, H-7, *J* 17.5 Hz, *J* 10.0 Hz, *J* 7.5 Hz, *J* 5.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-10 or C-11), 18.1 (C-11 or C-10), 28.0 (C-9), 35.7 (C-3), 43.2 (C-6), 67.3 (C-5), 78.4 (C-4), 119.0 (C-8), 131.3 (C-7), 169.7 (C-2). ***m/z*** (ES+) 213 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{16}N_2O_3Na^+$) requires ***m/z*** 235.1053, found ***m/z*** 235.1053.

A.1.5.5. 5-Isopropyl-1-(2-naphthylmethyl)-4-nitropyrrolidin-2-one 172ae



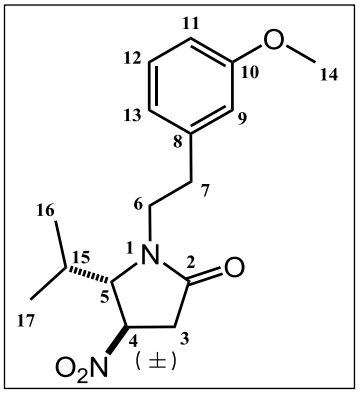
Prepared according to the general procedure **A**.

172ae (180 mg, 77%, single diastereomer) was obtained after purification by flash column chromatography (diethyl ether) as an off-white oil (R_f = 0.19 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1696 (C=O), 1598 (aromatic C=C), 1555 (NO_2), 1511 (aromatic C=C), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.80 (d, 3H, H-18 or H-19, *J* 7.0 Hz), 0.96 (d, 3H, H-19 or H-18, *J* 7.0 Hz), 2.25 (septd, 1H, H-17, *J* 7.0 Hz, *J* 3.5 Hz), 2.90 (ddd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz, *J* 1.5 Hz), 3.17 (dd, 1H, H-3', *J* 18.5 Hz, *J* 1.5 Hz), 3.54 (dd, 1H, H-5, *J* 3.5 Hz, *J* 1.5 Hz), 4.31 (d, 1H, H-6', *J* 15.0 Hz), 4.79 (dt, 1H, H-4, *J* 8.5 Hz, *J* 1.5 Hz), 5.66 (d, 1H, H-6', *J* 15.0 Hz), 7.37 (d, 1H, H_{Ar}, *J* 7.0 Hz), 7.42 (t, 1H, H_{Ar}, *J* 7.0 Hz), 7.50-7.59 (m, 2H, H-11 and H-12), 7.82-7.89 (m, 2H, H-8 and H-9),

7.99 (d, 1H, H_{Ar}, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.7 (C-18 or C-19), 18.1 (C-19 or C-18), 27.7 (C-17), 35.8 (C-3), 42.8 (C-6), 67.1 (C-5), 78.0 (C-4), 123.3 (C_{Ar}-H), 125.0 (C_{Ar}-H), 126.3 (C_{Ar}-H), 126.9 (C_{Ar}-H), 127.0 (C_{Ar}-H), 128.7 (C_{Ar}-H), 129.3 (C_{Ar}-H), 130.1 (C_{quat}), 131.3 (C_{quat}), 133.7 (C_{quat}), 169.8 (C-2). ***m/z*** (ES-) 311 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}N_2O_3Na^+$) requires ***m/z*** 335.1366, found ***m/z*** 335.1356.

A.1.5.6. 5-Isopropyl-1-[2-(3-methoxyphenyl)ethyl]-4-nitropyrrolidin-2-one 172af

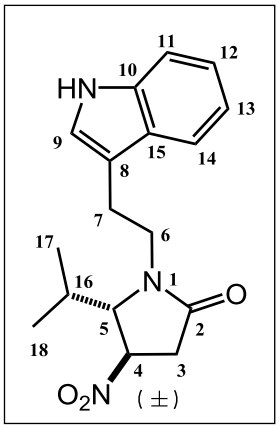


Prepared according to the general procedure **A**.

172af (193 mg, 84%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:3 petroleum ether / diethyl ether to pure diethyl ether) as a yellow oil (R_f = 0.14 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1698 (C=O), 1601 (aromatic C=C), 1556 (NO_2), 1556 (aromatic C=C), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.76 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 1.04 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 2.17 (septd, 1H, H-15, *J* 7.0 Hz, *J* 4.0 Hz), 2.76 (dd, 1H, H-3, *J* 18.5 Hz, *J* 9.0 Hz), 2.79-2.86 (m, 1H, H-7), 2.88-2.96 (m, 1H, H-7'), 3.06 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.11 (dt, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz), 3.82 (dd, 1H, H-5, *J* 4.0 Hz, *J* 2.0 Hz), 3.83 (s, 3H, H-14), 3.98 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz, *J* 6.0 Hz), 4.75 (dt, 1H, H-4, *J* 9.0 Hz, *J* 2.0 Hz), 6.84 (d, 1H, H_{Ar}, *J* 7.5 Hz), 6.89 (td, 1H, H_{Ar}, *J* 7.5 Hz, *J* 1.0 Hz), 7.13 (dd, 1H, H_{Ar}, *J* 8.0 Hz, *J* 1.5 Hz), 7.22 (td, 1H, H_{Ar}, *J* 8.0 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-16 or C-17), 18.1 (C-17 or C-16), 28.0 (C-15), 28.3 (C-7), 35.4 (C-3), 40.3 (C-6), 55.2 (C-14), 67.8 (C-5), 78.3 (C-4), 110.2 (C_{Ar}-H), 120.7 (C_{Ar}-H), 126.4 (C-8), 128.1 (C_{Ar}-H), 130.5 (C_{Ar}-H), 157.4 (C-10), 170.1 (C-2). ***m/z*** (ES-) 305 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}N_2O_4Na^+$) requires ***m/z*** 329.1472, found ***m/z*** 329.1463.

A.1.5.7. 1-[2-(1H-Indol-3-yl)ethyl]-5-isopropyl-4-nitropyrrolidin-2-one 172ag

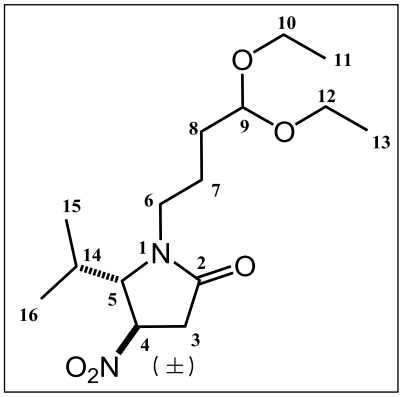


Prepared according to the general procedure **A**.

172ag (150 mg, 64%, single diastereomer) was obtained after purification by flash column chromatography (gradient from pure diethyl ether to 1:3 ethyl acetate / diethyl ether) as a orange-yellow oil (R_f = 0.18 in diethyl ether).

IR (cm^{-1}) ν_{max} 3308 (N-H), 1684 (C=O), 1556 (NO_2), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.72 (d, 3H, H-17 or H-18, *J* 7.0 Hz), 0.91 (d, 3H, H-18 or H-17, *J* 7.0 Hz), 2.10 (septd, 1H, H-16, *J* 7.0 Hz, *J* 4.0 Hz), 2.75 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 2.96-3.04 (m, 1H, H-7), 3.03-3.12 (m, 1H, H-7'), 3.06 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.23 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.5 Hz), 3.67 (dd, 1H, H-5, *J* 4.0 Hz, *J* 2.0 Hz), 4.06 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz, *5*.5 Hz), 4.70 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.0 Hz), 6.96 (d, 1H, H-9, *J* 2.0 Hz), 7.08-7.16 (m, 1H, H-13), 7.16-7.22 (m, 1H, H-12), 7.36 (d, 1H, H-11, *J* 8.0 Hz). 7.60 (d, 1H, H-14, *J* 8.0 Hz), 8.39 (br s, 1H, N-H).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-17 or C-18), 18.0 (C-18 or C-17), 23.4 (C-7), 28.3 (C-16), 35.5 (C-3), 40.8 (C-6), 68.2 (C-5), 78.5 (C-4), 111.4 (C-11), 111.9 (C-8), 118.4 (C-14), 119.4 (C13), 122.1 (C-12), 122.5 (C-9), 126.9 (C-15), 136.4 (C-10), 170.1 (C-2). ***m/z*** (ES-) 314 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{21}N_3O_3Na^+$) requires ***m/z*** 338.1475, found ***m/z*** 338.1472.

A.1.5.8. 1-(4,4-Diethoxybutyl)-5-isopropyl-4-nitropyrrolidin-2-one 172ah



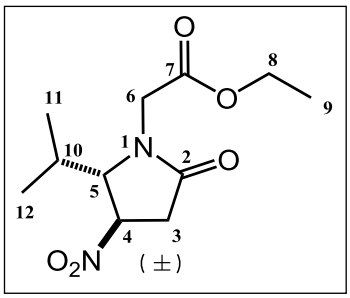
Prepared according to the general procedure **A**.

172ah (200 mg, 84%, single diastereomer) was obtained after purification by flash column chromatography (gradient from pure diethyl ether to 5:2 diethyl ether / ethyl acetate) as a light yellow oil (R_f = 0.11 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1697 (C=O), 1557 (NO_2), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-15 or H-16, *J* 7.0 Hz), 1.09 (d, 3H, H-16 or H-15, *J* 7.0 Hz), 1.18 (t, 6H, H-11 and H-13, *J* 7.0 Hz), 1.49-1.71 (m, 4H, H-7 and H-8), 2.19 (septd, 1H, H-14, *J* 7.0 Hz, *J* 3.5 Hz),

2.76-2.85 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 9.0 Hz, *J* 0.5 Hz), 2.85-2.94 (m, 1H, H-6), 3.03 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.0 Hz), 3.43-3.52 (m, 2H, H-10 or H-12), 3.58-3.67 (m, 2H, H-12 or H-10), 3.74 (dt, 1H, H-6', *J* 14.5 Hz, *J* 7.0 Hz), 3.98 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0Hz), 4.47 (t, 1H, H-9, *J* 5.0 Hz), 4.84 (dt, 1H, H-4, *J* 9.0 Hz, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-15 or C-16), 15.3 (C-11 and C-13), 18.1 (C-16 or C-15), 21.8 (C-7), 28.1 (C-14), 30.6 (C-8), 35.8 (C-3), 40.2 (C-6), 61.4 (C-10 or C-12), 61.5 (C-12 or C-10), 67.4 (C-5), 78.4 (C-4), 102.4 (C-9), 169.9 (C-2). ***m/z*** (ES-) 315 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{28}N_2O_5Na^+$) requires ***m/z*** 339.1890, found ***m/z*** 339.1884

A.1.5.9. Ethyl (2-isopropyl-3-nitro-5-oxopyrrolidin-1-yl)acetate 172ai

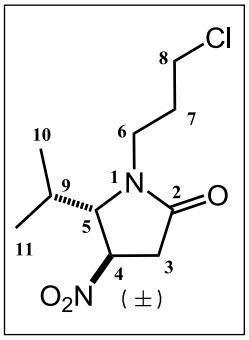


Prepared according to the general procedure **A**.

172ai (100 mg, 52%, single diastereomer and traces (5%) of the product of the elimation of the nitro group) was obtained after purification by flash column chromatography (gradient from 1:3 petroleum ether / diethyl ether to 10:1 diethyl ether / methanol) as a light yellow oil (R_f = 0.14 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1746 (C=O ester), 1706 (C=O amide), 1558 (NO_2), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 1.11 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 1.27 (t, 3H, H-9, *J* 7.5 Hz), 2.13 (septd, 1H, H-10, *J* 7.0 Hz, *J* 3.5 Hz), 2.86 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 3.18 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.71 (d, 1H, H-6, *J* 17.5 Hz), 4.15 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0 Hz), 4.16-4.23 (m, 2H, H-8), 4.42 (d, 1H, H-6', *J* 17.5 Hz), 4.85 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.0 (C-9), 15.3 (C-11 or C-12), 18.1 (C-12 or C-11), 28.6 (C-10), 34.8 (C-3), 42.5 (C-6), 61.7 (C-8), 68.3 (C-5), 78.5 (C-4), 167.8 (C-7), 170.6 (C-2). ***m/z*** (ES-) 257 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{18}N_2O_5Na^+$) requires ***m/z*** 281.1108, found ***m/z*** 281.1109.

A.1.5.10. 1-(3-Chloropropyl)-5-isopropyl-4-nitropyrrolidin-2-one 172aj

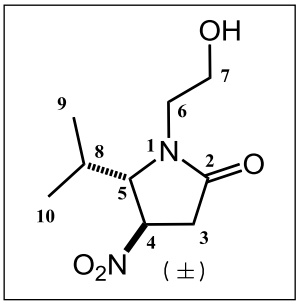


Prepared according to the general procedure **A**.

172aj (140 mg, 75%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:3 petroleum ether / diethyl ether to pure diethyl ether) as a yellow oil (R_f = 0.20 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1696 (C=O), 1556 (NO_2), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.81 (d, 3H, H-10 or H-11, *J* 7.0 Hz), 1.12 (d, 3H, H-11 or H-10, *J* 7.0 Hz), 1.92-2.03 (m, 1H, H-7), 2.10-2.18 (m, 1H, H-7'), 2.18-2.28 (septd, 1H, H-9, *J* 7.0 Hz, *J* 4.0 Hz), 2.82 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 3.01 (dd, 1H, H-3', *J* 18.5 Hz, *J* 1.5 Hz), 3.12 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.58 (t, 2H, H-8, *J* 6.5 Hz), 3.80 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz, *J* 6.0 Hz), 3.99 (dd, 1H, H-5, *J* 4.0 Hz, *J* 1.5 Hz), 4.86 (dt, 1H, H-4, *J* 8.5 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 15.0 (C-10 or 11), 18.2 (C-11 or 10), 28.5 (C-9), 29.7 (C-7), 35.8 (C-3), 38.2 (C-6), 42.0 (C-8), 68.2 (C-5), 78.6 (C-4), 170.2 (C-2). ***m/z*** (ES-) 247 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{17}ClN_2O_3Na^+$) requires ***m/z*** 271.0820, found ***m/z*** 271.0827.

A.1.5.11. 1-(2-Hydroxyethyl)-5-isopropyl-4-nitropyrrolidin-2-one 172ak



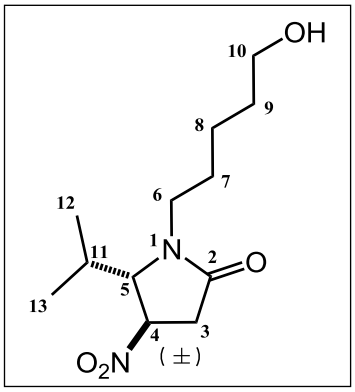
Prepared according to the general procedure **A**.

172ak (100 mg, 25%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:1 to 1:5 petroleum ether / diethyl ether) as a light yellow amorphous solid (R_f = 0.68 in diethyl ether).

IR (cm^{-1}) ν_{max} 3400 (OH), 1682 (C=O), 1557 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.82 (d, 3H, H-9 or H-10, *J* 7.0 Hz), 1.10 (d, 3H, H-10 or H-9, *J* 7.0 Hz), 2.24 (septd, 1H, H-8, *J* 7.0 Hz, *J* 4.0 Hz), 2.85 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 3.07 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.21 (ddd, 1H, H-6, *J* 14.5 Hz, *J* 6.5 Hz, *J* 4.5 Hz), 3.71 (ddd, 1H, H-6', *J* 14.5 Hz, *J* 9.5 Hz, *J* 5.0 Hz), 3.75-3.87 (m, 2H, H-7), 4.13 (dd, 1H, H-5, *J* 4.0 Hz, *J* 2.0 Hz), 4.86 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 15.1

(C-9 or C-10), 18.2 (C-10 or C-9), 28.6 (C-8), 35.7 (C-3), 44.3 (C-6), 61.0 (C-7), 69.4 (C-5), 78.8 (C-4), 171.3 (C-2). ***m/z*** (ES-) 215 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_9H_{16}N_2O_4Na^+$) requires ***m/z*** 239.1002, found ***m/z*** 239.1001.

A.1.5.12. 1-(5-Hydroxypentyl)-5-isopropyl-4-nitropyrrolidin-2-one 172al

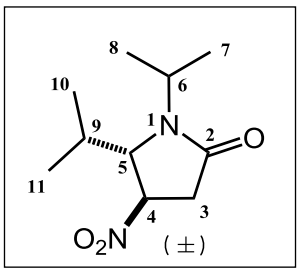


Prepared according to the general procedure **A**.

172al (150 mg, 78%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:5 to 1:1 ethyl acetate / diethyl ether) as a yellow oil (R_f = 0.26 in ethyl acetate / diethyl ether 1:1).

IR (cm^{-1}) ν_{max} 3421 (OH), 1686 (C=O), 1557 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-12 or H-13, *J* 7.0 Hz), 1.10 (d, 3H, H-13 or H-12, *J* 7.0 Hz), 1.30-1.43 (m, 2H, H-8), 1.46-1.65 (m, 4H, H-7 and H-9), 2.18 (septd, 1H, H-11, *J* 7.0 Hz, *J* 4.0 Hz), 2.80 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 2.86 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 5.0 Hz), 3.02 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.61 (t, 2H, H-10, *J* 6.5 Hz), 3.74 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.96 (dd, 1H, H-5, *J* 4.0 Hz, *J* 2.0Hz), 4.84 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-12 or C-13), 18.2 (C-13 or C-12), 22.7 (C-8), 26.5 (C-7), 28.2 (C-11), 32.0 (C-9), 35.9 (C-3), 40.3 (C-6), 62.4 (C-10), 67.5 (C-5), 78.5 (C-4), 170.0 (C-2). ***m/z*** (ES-) 257 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{12}H_{22}N_2O_4Na^+$) requires ***m/z*** 281.1472, found ***m/z*** 281.1471.

A.1.5.13. 1,5-Diisopropyl-4-nitropyrrolidin-2-one 172am

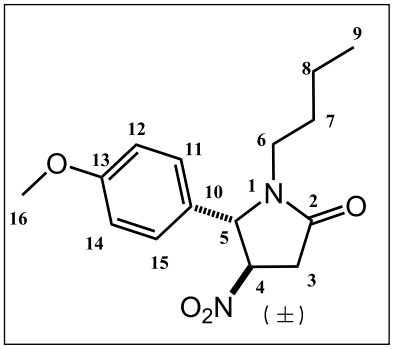


Prepared according to the general procedure **A**.

172am (100 mg, 63%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:1 to 1:5 petroleum ether / diethyl ether) as a light yellow amorphous solid (R_f = 0.68 in diethyl ether).

mp 58-60 °C. **IR** (cm^{-1}) ν_{max} 1695 (C=O), 1556 (NO_2), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.83 (d, 3H, H-10 or H-11, *J* 7.0 Hz), 1.11 (d, 3H, H-11 or H-10, *J* 7.0 Hz), 1.27 (d, 3H, H-7 or H-8, *J* 7.0 Hz), 1.29 (d, 3H, H-8 or H-7, *J* 7.0 Hz), 2.16 (septd, 1H, H-9, *J* 7.0 Hz, *J* 3.0 Hz), 2.79 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.0 Hz), 2.96 (dd, 1H, H-3', *J* 18.5 Hz, *J* 1.0 Hz), 3.98 (dd, 1H, H-5, *J* 3.0 Hz, *J* 1.0 Hz), 4.04 (sept, 1H, H-6, *J* 7.0 Hz), 4.79 (dt, 1H, H-4, *J* 8.0 Hz, *J* 1.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.8 (C-10 or C-11), 18.6 (C-11 or C-10), 19.0 (C-7 or C-8), 21.0 (C-8 or C-7), 30.7 (C-9), 36.4 (C-3), 45.5 (C-6), 68.0 (C-5), 78.8 (C-4), 170.0 (C-2). ***m/z*** (ES+) 215 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}N_2O_3^+$) requires ***m/z*** 215.1390, found ***m/z*** 215.1400.

A.1.5.14. 1-Butyl-5-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 172ba

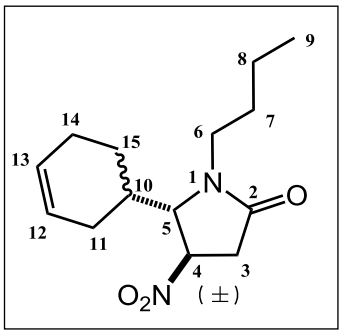


Prepared according to the general procedure **A**.

172ba (190 mg, 87%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 2:1 to 1:1 petroleum ether / diethyl ether) as a dark yellow amorphous solid (R_f = 0.21 in petroleum ether / diethyl ether 1:1).

mp 58-62 °C. **IR** (cm^{-1}) ν_{max} 1700 (C=O), 1612 (C=C aromatic), 1556 (NO_2), 1514 (C=C aromatic), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.88 (t, 3H, H-9, *J* 7.5 Hz), 1.19-1.36 (m, 2H, H-8), 1.44 (quint, 2H, H-7, *J* 7.5 Hz), 2.62 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.5 Hz), 3.04 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 0.5 Hz), 3.13 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.5 Hz), 3.77 (dt, 1H, H-6', *J* 14.0 Hz, *J* 7.5 Hz), 3.83 (s, 1H, H-16), 4.86 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.5 Hz), 5.09 (d, 1H, H-5, *J* 2.5 Hz), 6.93-6.98 (m, 2H, H-12 and H-14), 7.11-7.16 (m, 2H, H-11 and H-15). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.6 (C-3), 40.5 (C-6), 55.4 (C-16), 65.6 (C-5), 85.1 (C-4), 115.0 (C-12 and C-14), 127.5 (C-11 and C-15), 128.1 (C-10), 160.4 (C-13), 169.8 (C-2). ***m/z*** (ES-) 291 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}N_2O_2Na^+$) requires ***m/z*** 315.1315, found ***m/z*** 315.1320.

A.1.5.15. 1-Butyl-5-(cyclohex-3-en-1-yl)-4-nitropyrrolidin-2-one 172ca (as an inseparable mixture of two diastereomers)



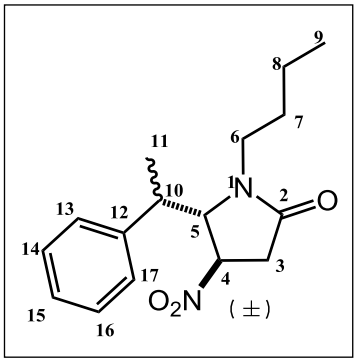
Prepared according to the general procedure **A**.

172ca (150 mg, 75%, dr 1:1) was obtained after purification by flash column chromatography (gradient from 1:1 to 1:2 petroleum ether / diethyl ether) as an off-white solid (R_f = 0.29 in diethyl ether / petroleum ether 4:3).

mp 122-124 °C. **IR** (cm^{-1}) ν_{max} 1696 (C=O), 1556 (NO_2), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.93 (t, 3H, H-9, *J* 7.5 Hz, one diastereomer), 0.94 (t, 3H, H-9, *J* 7.5 Hz, other diastereomer), 1.07 (qd, 1H, H-15, *J* 11.5 Hz, *J* 6.0 Hz), 1.25-1.38 (m, 4H, H-8, both diastereomers), 1.42-1.56 (m, 4H + 2H, 4 x H-7 both diastereomers, H-15 and/or H-11), 1.57-1.65 (m, 2H, H-15), 1.74-1.81 (m, 1H, H-14), 1.88-1.94 (m, 1H, H-14), 2.00-2.30 (m, 7H, 2x H-10, 2x H-11, 2x H-14', H-11 or H-15), 2.77-2.93 (m, 4H, 2x H-6, 2xH-3), 3.06 (ddd, 2H, H-3' both diastereomers, *J* 18.5 Hz, *J* 3.0 Hz, *J* 2.5 Hz), 3.75 (ddd, 1H, H-6' of one diastereomers, *J* 13.5 Hz, *J* 8.5 Hz, *J* 7.0 Hz), 3.80 (dt, 1H, H-6' of other diastereomer, *J* 13.5 Hz, *J* 8.0 Hz), 4.03 (dd, 1H, H-5 of one diastereomer, *J* 3.0 Hz, *J* 1.5 Hz), 4.05 (dd, 1H, H-5 of other diastereomer, *J* 4.0 Hz, *J* 2.0 Hz), 4.86 (dt, 1H, H-4 of one diastereomer, *J* 8.5 Hz, *J* 1.5 Hz), 4.90 (dt, 1H, H-4 of other diastereomer, *J* 9.0 Hz, *J* 2.0 Hz), 5-64-5.68 (m, 1H, H-12 or H-13), 5.70-5.78 (m, 3H, H-12 and H-13).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9 of both diastereomers), 19.9 (C-8 of both diastereomers), 21.8 (C-15), 24.9 (C-11, C-14, C-15'), 27.4 (C-11'), 28.8 (C-7), 28.9 (C-7'), 34.5 (C-10), 34.7 (C-10'), 35.7 (C-3), 35.9 (C-3), 40.3 (C-6), 40.5 (C-6'), 66.4 (C-5), 66.8 (C-5'), 79.1 (C-4), 79.3 (C-4'), 124.5, 125.1, 127.2, 127.6 (C-12 and C-13 for both diastereomers), 169.6 (C-2), 169.9 (C-2').***m/z*** (ES-) 265 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{22}N_2O_3Na^+$) requires ***m/z*** 289.1523, found ***m/z*** 289.1527.

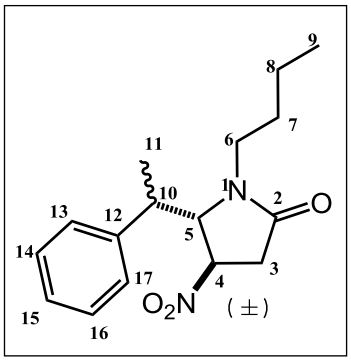
A.1.5.16. 1-Butyl-4-nitro-5-(1-phenylethyl)pyrrolidin-2-one 172da

Prepared according to the general procedure **A**. **172da** (156 mg, 72%, dr 4:1) was obtained as a separable mixture of two diastereoisomers. The purification was achieved by flash column chromatography (diethyl ether, R_{f1} = 0.20, R_{f2} = 0.05).



Major diastereoisomer, isolated as an orange solid.

mp 93-96 °C. **IR** (cm^{-1}) ν_{max} 1699 (C=O), 1556 (NO_2), 1497 (C=C aromatic), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.95 (t, 3H, H-9, *J* 7.5 Hz), 1.28-1.45 (m, 3H, H-8 and H-3), 1.54 (d, 3H, H-11, *J* 7.0 Hz), 1.56-1.61 (m, 2H, H-7), 2.58 (dd, 1H, H-3', *J* 18.0 Hz, *J* 1.0 Hz), 3.02 (dt, 1H, H-6, *J* 14.0 Hz, *J* 6.5 Hz), 3.33 (qd, 1H, H-10, *J* 7.0 Hz, *J* 3.0 Hz), 3.97 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.17 (d, 1H, H-5, *J* 3.0 Hz), 4.74 (d, 1H, H-4, *J* 8.0 Hz), 7.10 (d, 2H, H-13 and H-17), 7.28-7.39 (m, 3H, H-14, H-15 and H-16). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 15.6 (C-11), 19.8 (C-8), 28.9 (C-7), 34.6 (C-3), 37.8 (C-10), 40.4 (C-6), 67.4 (C-5), 79.6 (C-4), 127.5 (C-13 and C-17), 128.0 (C-15), 129.0 (C-14 and C-16), 137.9 (C-12), 170.3 (C-2). ***m/z*** (ES-) 289 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2O_3^+$) requires ***m/z*** 291.1703, found ***m/z*** 291.1702.

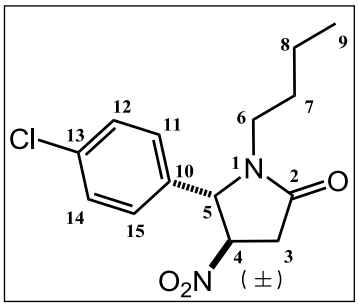


Minor diastereomer, isolated as an orange oil.

IR (cm^{-1}) ν_{max} 1700 (C=O), 1555 (NO_2), 1496 (C=C aromatic), 1360 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.93 (t, 3H, H-9, *J* 7.5 Hz), 1.27 (d, 3H, H-11, *J* 7.0 Hz), 1.29-1.39 (m, 2H, H-8), 1.48-1.64 (m, 2H, H-7), 2.67-2.76 (m, 2H, H-3 and H-6), 2.90 (dd, 1H, H-3', *J* 18.5 Hz, *J* 1.0 Hz), 3.26-3.33 (m, 1H, H-10), 3.82 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.34 (dd, 1H, H-5, *J* 5.0 Hz, *J* 1.0 Hz), 4.82 (dt, 1H, H-4, *J* 8.5 Hz, *J* 1.0 Hz), 7.24 (d, 2H, H-13 and H-17), 7.29-7.34 (m, 1H, H-15), 7.35-7.42 (m, 2H, H-14 and H-16). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9 or C-11), 13.7 (C-11 or C-9), 19.8 (C-8), 28.8 (C-7), 35.9 (C-3), 40.2 (C-10), 40.7 (C-6), 67.2 (C-5), 79.6 (C-4), 127.5 (C-13 and C-17), 127.8 (C-15), 129.1 (C-14 and C-16), 139.4 (C-12), 170.2 (C-2). ***m/z*** (ES-) 289 ($[M-H]^-$, 100%),

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}N_2O_3Na^+$) requires ***m/z*** 313.1523, found ***m/z*** 313.1525.

A.1.5.17. 1-Butyl-5-(4-chlorophenyl)-4-nitropyrrolidin-2-one 172ea

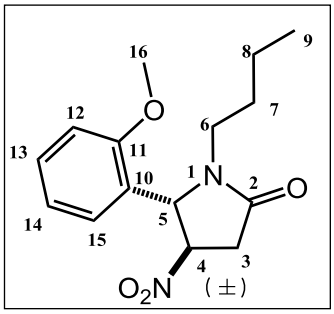


Prepared according to the general procedure **A**.

172ea (160 mg, 72%, dr 10:1) was obtained after purification by flash column chromatography (gradient from 2:1 petroleum ether / diethyl ether to pure diethyl ether) as an orange oil (R_f = 0.23 in petroleum ether / diethyl ether 1:1).

IR (cm^{-1}) ν_{max} 1702 (C=O), 1557 (NO_2), 1492 (C=C aromatic), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89 (t, 3H, H-9, *J* 7.0 Hz), 1.18-1.36 (m, 2H, H-8), 1.40-1.49 (m, 2H, H-7), 2.61 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.02 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 0.5 Hz), 3.16 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.5 Hz), 3.79 (dt, 1H, H-6', 14.0 Hz, 8.0 Hz), 4.84 (dt, 1H, H-4, 8.0 Hz, 2.5 Hz), 5.14 (d, 1H, H-5, 2.5 Hz), 7.15-7.22 (m, 2H, H-11 and H-15), 7.41-7.47 (m, 2H, H-12 and H-14). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.4 (C-3), 40.6 (C-6), 65.3 (C-5), 84.7 (C-4), 127.6 (C-15 and 11), 129.9 (C-12 and C-14), 134.9 (C-10), 135.5 (C-13), 169.8 (C-2). ***m/z*** (ES-) 295 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}ClN_2O_3^+$) requires ***m/z*** 297.1000, found ***m/z*** 297.1006.

A.1.5.18. 1-Butyl-5-(2-methoxyphenyl)-4-nitropyrrolidin-2-one 172fa



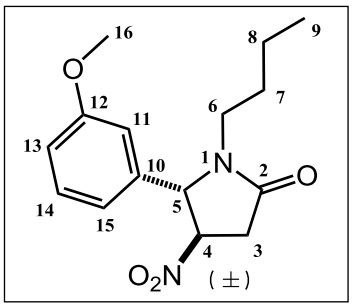
Prepared according to the general procedure **A**.

172fa (183 mg, 83%, >98:2) was obtained after purification by flash column chromatography (gradient from 2:1 to 1:1 petroleum ether / diethyl ether) as a yellow oil (R_f = 0.25 in petroleum / diethyl ether 1:1).

IR (cm^{-1}) ν_{max} 1701 (C=O), 1602 cm^{-1} (C=C aromatic), 1556 cm^{-1} (NO_2), 1492 cm^{-1} (C=C aromatic), 1367 cm^{-1} (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89 (t, 3H, H-9, *J* 7.5 Hz), 1.21-1.38 (m, 2H, H-8), 1.47 (quint, 2H, H-7, *J* 7.5 Hz), 2.65 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.5 Hz), 2.98-3.01 (m, 2H, H-3), 3.75-3.84 (m, 1H, H-

6'), 3.87 (s, 1H, H-16), 4.91-4.96 (m, 1H, H-4), 5.42 (br s, 1H, H-5), 6.95-7.04 (m, 3H, H_{Ar}), 7.35-7.40 (m, 1H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 19.8 (C-8), 28.9 (C-7), 35.6 (C-3), 40.8 (C-6), 55.5 (C-16), 61.8 (C-5), 83.6 (C-4), 111.1 (C_{Ar}-H), 120.9 (C_{Ar}-H), 123.9 (C-10), 127.0 (C-15), 130.5 (C_{Ar}-H), 156.9 (C-11), 170.6 (C-2). ***m/z*** (ES-) 291 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}N_2O_4Na^+$) requires ***m/z*** 315.1315, found ***m/z*** 315.1315.

A.1.5.19. 1-Butyl-5-(3-methoxyphenyl)-4-nitropyrrolidin-2-one 172ga

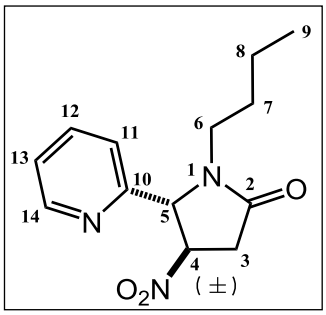


Prepared according to the general procedure **A**.

172ga (190 mg, 87%, 93:7) was obtained after purification by flash column chromatography (gradient from 2:1 to 1:1 petroleum ether / diethyl ether) as a yellow oil (R_f = 0.32 in petroleum ether / diethyl ether 1:1).

IR (cm^{-1}) ν_{max} 1702 (C=O), 1602 (C=C aromatic), 1557 (NO_2), 1492 (C=C aromatic), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89 (t, 3H, H-9, *J* 7.5 Hz), 1.29 (sext, 2H, H-8, *J* 7.5 Hz), 1.46 (quint, 2H, H-7, *J* 7.5 Hz), 2.66 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.5 Hz), 3.04 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 0.5 Hz), 3.13 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.5 Hz), 3.76-3.82 (m, 1H, H-6'), 3.83 (s, 1H, H-16), 4.87 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.5 Hz), 5.12 (d, 1H, H-5, *J* 2.5 Hz), 6.73 (t, 1H, H-11, *J* 2.0 Hz), 6.79 (d, 1H, H-15, *J* 8.0 Hz), 6.93 (dd, 1H, H-13, *J* 8.0 Hz, *J* 2.0 Hz), 7.36 (t, 1H, H-14, *J* 8.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.6 (C-3), 40.7 (C-6), 55.4 (C-16), 65.9 (C-5), 84.8 (C-4), 112.0 (C-11), 114.4 (C-13), 118.0 (C-15), 130.8 (C-14), 138.0 (C-10), 160.6 (C-12), 170.0 (C-2). ***m/z*** (ES-) 291 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}N_2O_4Na^+$) requires ***m/z*** 315.1315, found ***m/z*** 315.1313.

A.1.5.20. 1-Butyl-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one 172ha

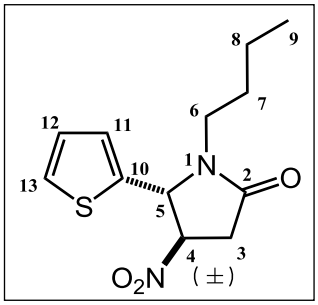


Prepared according to the general procedure **A**.

172ha (105 mg, 53%, > 98:2) was obtained after purification by flash column chromatography (diethyl ether) as a dark brown oil (R_f = 0.40 in diethyl ether).

IR (cm^{-1}) ν_{max} 1699 (C=O), 1591 (C=C aromatic), 1555 (NO_2), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (t, 3H, H-9, *J* 7.5 Hz), 1.18-1.33 (m, 2H, H-8), 1.34-1.49 (m, 2H, H-7), 2.60 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 5.5 Hz), 3.11 (dd, 1H, H-3, *J* 17.5 Hz, *J* 2.5 Hz), 3.22 (dd, 1H, H-3', *J* 17.5 Hz, *J* 8.5 Hz), 3.69 (dt, 1H, H-6', *J* 14.0 Hz, 8.0 Hz), 5.17 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.5 Hz), 5.21 (d, 1H, H-5, 2.5 Hz), 7.27 (d, 1H, H-11, *J* 8.0 Hz), 7.32 (ddd, 1H, H-13, *J* 8.0 Hz, *J* 5.0 Hz, *J* 1.0 Hz), 7.76 (td, 1H, H-12, *J* 8.0 Hz, *J* 2.0 Hz), 8.64 (d, 1H, H-14, *J* 5.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.9 (C-7), 35.3 (C-3), 40.7 (C-6), 66.5 (C-5), 83.1 (C-4), 122.1 (C-11), 124.1 (C-13), 137.3 (C-12), 151.0 (C-14), 155.4 (C-10), 170.4 (C-2). ***m/z*** (ES-) 262 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{17}N_3O_3Na^+$) requires ***m/z*** 286.1162, found ***m/z*** 286.1159.

A.1.5.21. 1-Butyl-4-nitro-5-(2-thienyl)pyrrolidin-2-one 172ia



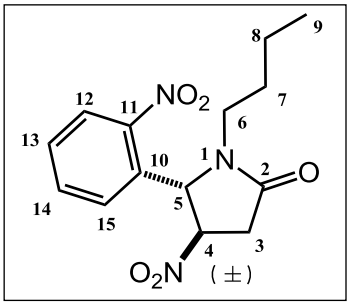
Prepared according to the general procedure **A**.

172ia (151 mg, 75%, dr 10:1) was obtained after purification by flash column chromatography (gradient from 2:1 petroleum ether / diethyl ether to pure diethyl ether) as a colorless solid (R_f = 0.16 in petroleum ether / diethyl ether 1:1). The poduct was recrystallised from ethyl acetate / petroleum ether 1:3.

mp 97.3-98.9 °C. **IR** (cm^{-1}) ν_{max} 1699 (C=O), 1555 (NO_2), 1364 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.90 (t, 3H, H-9, *J* 7.5 Hz), 1.22-1.35 (m, 2H, H-8), 1.42-1.52 (m, 2H, H-7), 2.76 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 6.0 Hz), 3.12-3.17 (m, 2H, H-3), 3.76 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.99 (ddd, 1H, H-4, *J* 7.0 Hz, *J* 4.5 Hz, *J* 2.0 Hz), 5.45 (d, 1H, H-5, *J* 2.0 Hz), 7.03-7.06 (m, 1H, H-12), 7.07-7.10 (m, 1H, H-11 or H-

13), 7.38 (dd, 1H, H-11 or H-13, *J* 5.0 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.9 (C-7), 34.6 (C-3), 40.6 (C-6), 61.6 (C-5), 84.9 (C-4), 126.8 (C-11), 126.9 (C-12), 127.6 (C-13), 139.7 (C-10), 169.1 (C-2). ***m/z*** (ES-) 267 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}N_2O_3S^+$) requires ***m/z*** 269.0954, found ***m/z*** 269.0964.

A.1.5.22. 1-Butyl-4-nitro-5-(3-nitrophenyl)pyrrolidin-2-one 172ja



Prepared according to the general procedure **A**.

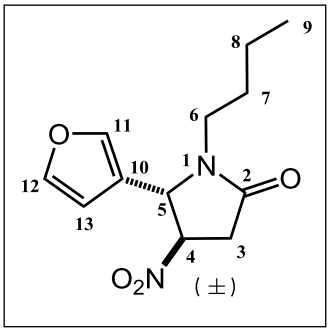
172ja (160 mg, 70%, dr 98:2) was obtained after purification by flash column chromatography (gradient from 1:2 petroleum ether / diethyl ether to 5:1 diethyl ether / ethyl acetate) as a brown oil (R_f = 0.22 in diethyl ether).

IR (cm^{-1}) ν_{max} 1702 (C=O), 1609 (C=C aromatic), 1558 (NO_2), 1529 (C=C aromatic), 1349 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.90 (t, 3H, H-9, *J* 7.5 Hz), 1.21-1.43 (m, 2H, H-8), 1.43-1.61 (m, 2H, H-7), 2.57 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz, *J* 5.5 Hz), 2.93 (br d, 1H, H-3, *J* 18.5 Hz), 3.07 (dd, 1H, H-3', *J* 18.5 Hz, *J* 8.5 Hz), 3.88 (dt, 1H, H-6', 14.0 Hz, 8.0 Hz), 5.04 (br d, 1H, H-4, 8.5 Hz), 5.86 (br s, 1H, H-5), 7.27 (d, 1H, H_{Ar}, *J* 8.0 Hz), 7.63 (td, 1H H_{Ar}, *J* 8.0 Hz, *J* 1.0 Hz), 7.75 (td, 1H, H_{Ar}, *J* 8.0 Hz, *J* 1.0 Hz), 8.21 (d, 1H, H_{Ar}, *J* 8.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.9 (C-8), 28.8 (C-7), 35.6 (C-3), 41.2 (C-6), 61.3 (C-5), 83.3 (C-4), 126.5 (C-12 and C-15), 130.4 (C_{Ar}-H), 131.7 (C-10), 134.7 (C_{Ar}-H), 148.0 (C-11), 170.7 (C-2). ***m/z*** (ES-) 306 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{17}N_3O_5Na^+$) requires ***m/z*** 330.1060, found ***m/z*** 330.1071.

A.1.5.23. 1-Butyl-5-(3-furyl)-4-nitropyrrolidin-2-one 172ka

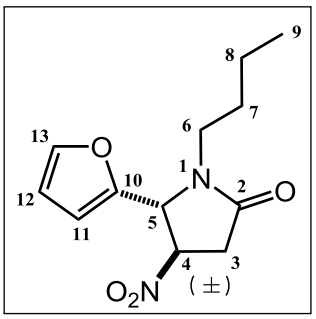
Prepared according to the general procedure **A**.

172ka (165 mg, 70%, dr 9:1) was obtained after purification by flash column chromatography (petroleum ether / diethyl ether 1:3) as a brown oil (R_f = 0.23 in petroleum / diethyl ether 2:5).



IR (cm^{-1}) ν_{max} 1699 (C=O), 1557 (NO_2), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89 (t, 3H, H-9, *J* 7.5 Hz), 1.18-1.35 (m, 2H, H-8), 1.37-1.52 (m, 2H, H-7), 2.72 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 7.5 Hz, *J* 6.0 Hz), 3.09 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 0.5 Hz), 3.13 (dd, 1H, H-3', *J* 18.0 Hz, *J* 3.5 Hz), 3.71 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.92 (dt, 1H, H-4, *J* 8.0 Hz, *J* 3.5 Hz), 5.13 (d, 1H, H-5, *J* 2.5 Hz), 6.29 (dd, 1H, H-13, *J* 1.5 Hz, *J* 1.0 Hz), 7.48 (s, 1H, H-11), 7.49 (t, 1H, H-12, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.9 (C-7), 34.8 (C-3), 40.4 (C-6), 58.0 (C-5), 84.1 (C-4), 107.7 (C-13), 121.7 (C-10), 140.8 (C-11), 145.2 (C-12), 169.2 (C-2). ***m/z*** (ES-) 251 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{16}N_2O_4Na^+$) requires ***m/z*** 275.1002, found ***m/z*** 275.1006.

A.1.5.24. 1-Butyl-5-(2-furyl)-4-nitropyrrolidin-2-one 172la

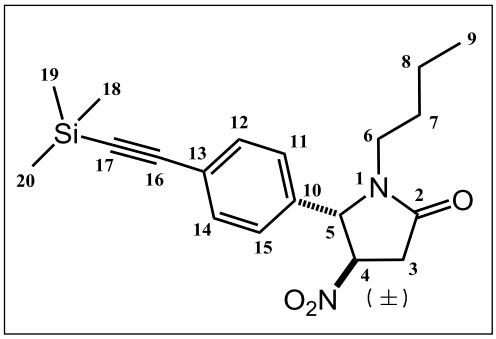


Prepared according to the general procedure **A**.

172la (120 mg, 65%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:1 petroleum ether / diethyl ether to pure diethyl ether) as a brown oil (R_f = 0.35 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1703 (C=O), 1557 (NO_2), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.88 (t, 3H, H-9, *J* 7.5 Hz), 1.22-1.32 (m, 2H, H-8), 1.32-1.40 (m, 1H, H-7), 1.40-1.49 (m, 1H, H-7'), 2.75 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 5.5 Hz), 3.12 (dd, 1H, H-3, *J* 17.5 Hz, *J* 3.5 Hz), 3.19 (dd, 1H, H-3', *J* 17.5 Hz, *J* 8.0 Hz), 3.60 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 8.5 Hz, *J* 7.0 Hz), 5.12 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.5 Hz), 5.21 (d, 1H, H-5, *J* 2.5 Hz), 6.39 (dd, 1H, H-12, *J* 3.5 Hz, *J* 12.0 Hz), 6.43 (d, 1H, H-11, *J* 3.5 Hz), 7.44 (d, 1H, H-13, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.9 (C-7), 35.2 (C-3), 40.6 (C-6), 59.3 (C-5), 81.9 (C-4), 110.2 (C-11), 110.8 (C-12), 144.0 (C-13), 148.1 (C-10), 169.4 (C-2). ***m/z*** (ES-) 251 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{16}N_2O_4Na^+$) requires ***m/z*** 275.1002, found ***m/z*** 275.1006.

A.1.5.25. 1-Butyl-4-nitro-5-{4-[(trimethylsilyl)ethynyl]phenyl}pyrrolidin-2-one 172ma

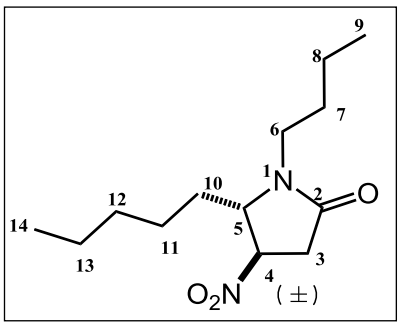


Prepared according to the general procedure **A**.

172ma (200 mg, 75%, single diastereomer) was obtained after purification by flash column chromatography (gradient from 1:1 petroleum ether / diethyl ether to pure diethyl ether) as a light brown oil (R_f = 0.53 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 2160 (C≡C), 1704 (C=O), 1557 (NO_2), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.24 (s, 9H, H-18, H-19 and H-20), 0.86 (t, 3H, H-9, *J* 7.5 Hz), 1.15-1.33 (m, 2H, H-8), 1.37-1.45 (m, 2H, H-7), 2.59 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.00 (dd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz), 3.11 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.5 Hz), 3.74 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.83 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.5 Hz), 5.12 (d, 1H, H-5, *J* 2.5 Hz), 7.15 (d, 2H, H-11 and H-15, *J* 8.5 Hz), 7.51 (d, 2H, H-12 and H-14, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C -0.2 (C-18, C-19 and C-20), 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.5 (C-3), 40.7 (C-6), 65.6 (C-5), 84.6 (C-4), 96.1 (C-17), 103.6 (C-16), 124.5 (C-13), 126.2 (C-11 and C-15), 133.1 (C-12 and C-14), 136.4 (C-10), 169.9 (C-2). ***m/z*** (ES-) 357 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{26}N_2O_3SiNa^+$) requires ***m/z*** 381.1605, found ***m/z*** 381.1613.

A.1.5.26. 1-Butyl-4-nitro-5-pentylpyrrolidin-2-one 172na



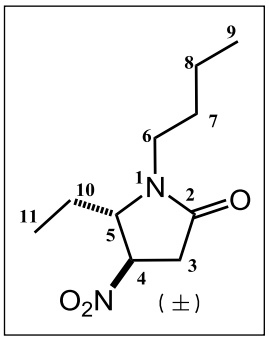
Prepared according to the general procedure **A**.

172na (86 mg, 45 %, single diastereomer) was obtained after purification by flash column chromatography (gradient from 5:1 to 1:1 petrol / ethyl acetate) as a light yellow oil (R_f = 0.50 in petroleum ether / ethyl acetate 1:1).

IR (cm^{-1}) ν_{max} 1699 (C=O), 1556 (NO_2), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89-0.99 (m, 6H, H-9 and H-14), 1.24-1.42 (m, 8H, H-8, H-11, H-12 and H-13), 1.42-1.58 (m, 3H, H-7 and H-10), 1.76-1.87 (m, 1H, H-10'), 2.80-2.93 (m, 2H, H-3 and H-6), 3.05 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.5 Hz), 3.73 (dt, 1H, H-

6', *J* 14.0 Hz, *J* 8.0 Hz), 4.05 (dt, 1H, H-5, *J* 8.0 Hz, *J* 2.5 Hz), 4.83 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9 or C-14), 13.9 (C-14 or C-9), 19.9 (C-8), 22.4 (C-13), 23.9 (C-11), 29.0 (C-7), 31.4 (C-10), 31.4 (C-12), 35.1 (C-3), 40.1 (C-6), 62.3 (C-5), 81.9 (C-4), 169.3 (C-2). ***m/z*** (ES-) 255 ([M-H]$^-$, 100%), HRMS (FI) exact mass calculated for $[M]^+$ ($C_{13}H_{24}N_2O_3$) requires ***m/z*** 256.1794, found ***m/z*** 256.1787.

A.1.5.27. 1-Butyl-5-ethyl-4-nitropyrrolidin-2-one 172oa



Prepared according to the general procedure **A** (on 50 mg of methyl 3-nitropropanoate).

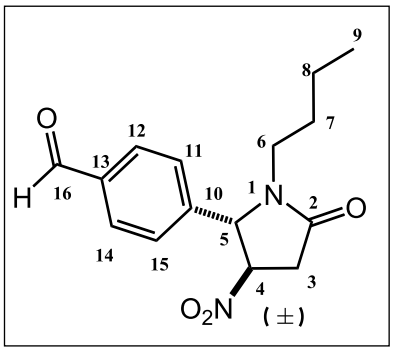
172oa (20 mg, 25%, single diastereomer) was obtained after purification by flash column chromatography (gradient from pure petroleum ether to pure diethyl ether) as a light yellow oil (R_f = 0.10 in petroleum ether / diethyl ether 2:5).

IR (cm^{-1}) ν_{max} 1697 (C=O), 1555 (NO_2), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.92 (t, 3H, H-9, *J* 7.5 Hz), 0.97 (t, 3H, H-11, *J* 7.5 Hz), 1.22-1.37 (m, 2H, H-8), 1.42-1.62 (m, 3H, H-10 and H-7), 1.89 (dqd, 1H, H-10', *J* 14.5 Hz, *J* 8.0 Hz, *J* 2.5 Hz), 2.81-2.92 (m, 2H, H-6 and H-3), 3.06 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.5 Hz), 3.73 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.02 (dt, 1H, H-5, *J* 8.0 Hz, *J* 2.5 Hz), 4.83 (dt, 1H, H-4, *J* 2.5 Hz, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 8.3 (C-11), 13.7 (C-9), 19.9 (C-8), 24.3 (C-10), 28.9 (C-7), 35.1 (C-3), 40.1 (C-6), 63.2 (C-5), 81.5 (C-4), 169.4 (C-2). ***m/z*** (ES-) 213 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}N_2O_3Na^+$) requires ***m/z*** 237.1210, found ***m/z*** 237.1215.

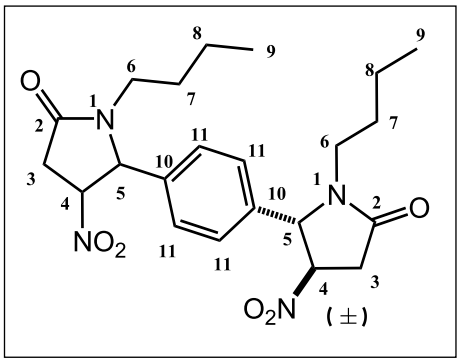
A.1.5.28. 4-(1-Butyl-3-nitro-5-oxopyrrolidin-2-yl)benzaldehyde 172pa and 5,5'-(1,4-phenylene)bis(1-butyl-4-nitropyrrolidin-2-one) 172qa

A 5 mL one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl-3-nitropropanoate (100 mg, 0.75 mmol, 1.0 eq), benzoic acid (138 mg, 1.13 mmol, 1.5 eq) and toluene (2 mL). The reaction mixture was pumped/filled three times with N_2 , then butylamine

(82 mg, 1.13 mmol, 1.5 eq) and terephthalaldehyde (75 mg, 0.56 mmol, 0.75 eq) were added *via* a microsyringe. The reaction was stirred at 70 °C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate (monitored by TLC). Upon completion, the crude mixture was concentrated under vacuum and the residue was taken up in dichloromethane , washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and purified by flash column chromatography. Two compounds were isolated: 5,5'-(1,4-phenylene)bis(1-butyl-4-nitropyrrolidin-2-one) (35 % yield), where both aldehyde underwent the nitro-Mannich / lactamization cascade and 4-(1-butyl-3-nitro-5-oxopyrrolidin-2-yl)benzaldehyde (14 % yield) where one of the aldehyde remained unreacted. They were isolated by flash column chromatography (gradient from diethyl ether to diethyl ether / ethyl acetate 1:1).



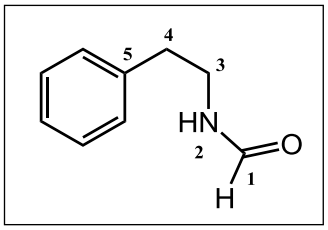
IR (cm^{-1}) ν_{max} 1700 (C=O), 1609 (C=C aromatic), 1556 (NO_2), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.88 (t, 3H, H-9, *J* 7.5 Hz), 1.20-1.35 (m, 2H, H-8), 1.41-1.50 (m, 2H, H-7), 2.63 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.04 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 3.19 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.5 Hz), 3.83 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.87 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.5 Hz), 5.26 (d, 1H, H-5, *J* 2.5 Hz), 7.43 (d, 2H, H-11 and H-15, *J* 8.0 Hz), 7.98 (d, 2H, H-12 and H-14, *J* 8.0 Hz), 10.05 (s, 1H, H-16). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.4 (C-3), 40.8 (C-6), 65.5 (C-5), 84.3 (C-4), 127.0 (C-11 and C-15), 130.9 (C-12 and C-14), 137.2 (C-13), 142.9 (C-10), 169.9 (C-2), 191.1 (C-16). ***m/z*** (ES-) 289 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_4Na^+$) requires ***m/z*** 313.1159, found ***m/z*** 313.1151.



IR (cm^{-1}) ν_{max} 1700 (C=O), 1557 (NO_2), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (t, 6H, H-9, *J* 7.5 Hz), 1.17-1.33 (m, 4H, H-8), 1.38-1.47 (m, 4H, H-7), 2.59 (dtd, 2H, H-6, *J* 14.0 Hz, *J* 7.0 Hz, *J* 2.0 Hz), 3.02 (ddd, 2H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 2.5 Hz), 3.13 (ddd, 2H, H-3', *J* 18.0 Hz, *J* 2.5 Hz, *J* 1.0 Hz), 3.79 (dt,

2H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.85 (dt, 2H, H-4, *J* 8.0 Hz, *J* 2.5 Hz), 5.18 (t, 2H, H-5, *J* 2.5 Hz), 7.32 (s, 4H, H-11). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.4 (C-3), 40.7 (C-6), 65.3 (C-5), 84.5 (C-4), 127.6 (C-11), 138.0 (C-10), 169.9 (C-2). ***m/z*** (ES-) 445 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{30}N_4O_6Na^+$) requires ***m/z*** 469.2058, found ***m/z*** 469.2059.

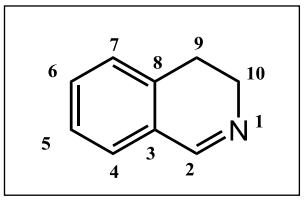
A.1.6. *N*-(2-phenylethyl)formamide



A 25 mL, one-necked flask, equipped with a magnetic stirrer bar, was charged with phenylethylamine (previously free based from the hydrochlorid salt: 5.0 g, 41 mmol, 1.0 eq) and ethylformate (8.3 mL, 103 mmol, 2.5 eq). The mixture was stirred at reflux overnight. Then, the excess ethylformate was removed under vacuum to give 6.4 g (> 99 % yield) of *N*-(2-phenylethyl)formamide as a pale yellow liquid which was used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.84 (t, 2H, H-4, *J* 7.0 Hz), 3.57 (q, 2H, H-3, *J* 7.0 Hz), 5.75 (br s, 1H, N-H), 7.16-7.23 (m, 2H, H_{Ar}), 7.23 - 7.28 (m, 1H, H_{Ar}), 7.29 - 7.35 (m, 2H, H_{Ar}), 8.10 (br s, 1H, H-1). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 35.5 (C-4), 39.2 (C-3), 126.6 (C_{Ar}-H), 128.6 (2x C_{Ar}-H), 128.7 (2x C_{Ar}-H), 138.5 (C-5), 161.2 (C-1).

A.1.7. 3,4-Dihydroisoquinoline 176a

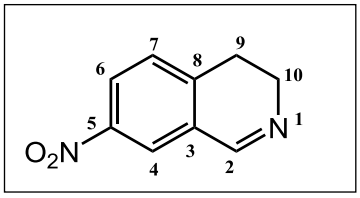


A 250 mL, one-necked flask, equipped with a magnetic stirrer bar, was charged with *N*-(2-phenylethyl)formamide (6.1 g, 41 mmol, 1.0 eq) and 115 % polyphosphoric acid (35 g). This was stirred at 160 °C overnight. Then, ice water was added to the reaction mixture and this was allowed to stir for an additional 2 hours. To this acidic mixture (pH = 1), a solution of 5M NaOH in water was added until pH = 14. The water layer was extracted three times with ethyl acetate; the combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum to give 4.2 g (80 % yield) of 3,4-

dihydroisoquinoline **176a** as a yellow oil which was purified by flash colum chromatography (ethyl acetate).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.75 (t, 2H, H-9, *J* 7.5 Hz), 3.78 (td, 2H, H-10, *J* 7.5 Hz, *J* 2.0 Hz), 7.16 (d, 1H, H_{Ar}, *J* 7.5 Hz), 7.25-7.33 (m, 2H, H_{Ar}), 7.35 (td, 1H, H_{Ar}, *J* 7.5 Hz, *J* 1.5 Hz), 8.34 (br s, 1H, H-2). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.0 (C-9), 47.4 (C-10), 127.1 (C_{Ar}-H), 127.2 (C_{Ar}-H), 127.4 (C_{Ar}-H), 128.5 (C_{quat}), 131.0 (C_{Ar}-H), 136.3 (C_{quat}), 160.3 (C-2).

A.1.8. 7-Nitro-3,4-dihydroisoquinoline 176b

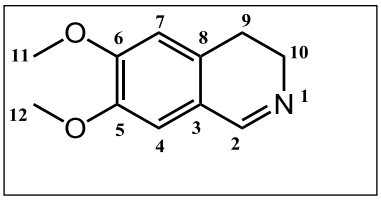


A solution of 3,4-dihydroquinoline (1.0 g, 7.5 mmol) in concentrated sulphuric acid (4.1 mL) was added dropwise to a stirred solution of potassium nitrate KNO_3 (0.8 g) in concentrated sulphuric acid (4.1 mL) at -10 °C. The mixture was allowed to warm up to room temperature over 2 hours, then it was heated to 60 °C for 4 hours. The mixture was poured on ice, neutralised with ammonium hydroxide (25% in water): a white solid precipitated which was extracted three times with dichloromethane. The organic layer was dried over Na_2SO_4, the solvent was evaporated under vacuum and the crude residue was purified by flash column chromatography (gradient from pure diethyl ether to pure ethyl acetate, R_f = 0.2 in diethyl ether).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.88 (t, 2H, H-9, *J* 7.5 Hz), 3.87 (td, 2H, H-10, *J* 7.5 Hz, *J* 2.0 Hz), 7.36 (d, 1H, H-7, *J* 8.0 Hz), 8.16 (d, 1H, H-4, *J* 2.0 Hz), 8.24 (dd, 1H, H-6, *J* 8.0 Hz, *J* 2.0 Hz), 8.44 (br s, 1H, H-2). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.1 (C-9), 46.8 (C-10), 121.8 (C-4), 125.7 (C-6), 128.6 (C-7), 143.5 (C-3 and C-8), 147.2 (C-5), 158.3 (C-2).

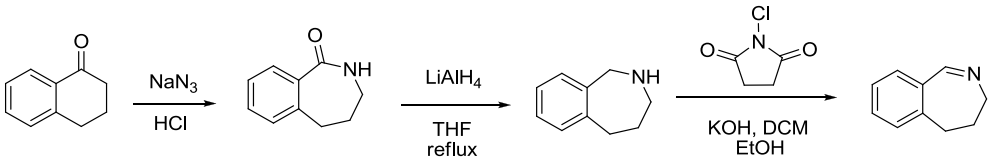
A.1.9. 7-Nitro-3,4-dihydroisoquinoline 176c

6,7-dimethoxy-3,4-dihydroisoquinoline **176c** was synthesized in two steps from 2-(3,4-dimethoxyphenyl)ethanamine according to the procedure used for the synthesis of 3,4-dihydroisoquinoline **176a**.



^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.68 (t, 2H, H-9, *J* 7.5 Hz), 3.73 (td, 2H, H-10, *J* 7.5 Hz, *J* 2.0 Hz), 3.90 (s, 3H, H-11 or H-12), 3.92 (s, 3H, H-12 or H-11), 6.67 (s, 1H, H-7), 6.81 (s, 1H, H-4), 8.23 (br s, 1H, H-2). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 24.7 (C-9), 47.3 (C-10), 56.1 (C-11 and C-12), 110.3 (C-4 and C-7), 121.5 (C-3), 129.8 (C-8), 147.8, 151.2 (C-5 and C-6), 159.6 (C-2).

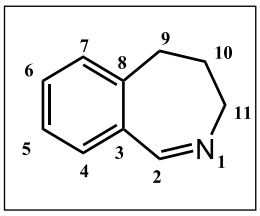
A.1.10. 7-Nitro-3,4-dihydroisoquinoline 176d



A suspension of α-tetralone (3.0 g, 20.5 mmol, 1 eq) in hydrochloric acid (30 mL) was cooled to 0 °C. Sodium azide (1.3 g, 20.5 mmol, 1 eq) was added and the mixture was stirred for 30 minutes at 0 °C, then at room temperature overnight behind a blastshield. The mixture was poured into ice-water and brought to pH = 9 by adding potassium carbonate. The product was extracted three times with dichloromethane, the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The purification was achieved by flash column chromatography and 2.1 g (64% yield) of 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (desired product) was isolated as a white solid (also, 1 g (33% yield) of its regioisomer was also isolated).

A 250 mL flask, flamed dried and purged with nitrogen, was charged with 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (2.0 g, 12.5 mmol, 1 eq) and dry THF (55 mL). To this, at 0 °C, was added dropwise a solution of lithium aluminium hydride 1M in THF (42 mL). The reaction mixture was heated to relfux overnight creating a white precipitate. Then, it was cooled to 0 °C and a 20% aqueous solution of KOH was added dropwise. The organic layer was decanted and the remaining solid was washed with diethyl ether. The combined organic layers were dried over Na_2SO_4, concentrated under vacuum and purified by flash column chromatography (diethyl ether / methanol / triethylamine 10:1:1) to give 1.8 g (99% yield) of 2,3,4,5-tetrahydro-1*H*-2-benzazepine as a light yellow oil.

2,3,4,5-tetrahydro-1*H*-2-benzazepine (1.6 g, 1 eq)) was dissolved in dichloromethane (30 mL) and *N*-chlorosuccinimide (1.5 g) was added. The mixture was stirred at room temperature for 30 minutes under nitrogen and then it was washed with water (2 x 10 mL), dried over Na_2SO_4 and added dropwise to a solution of potassium hydroxide in dry ethanol. The resulting mixture was stirred at room temperature until the starting material was consumed (monitored by TLC, about 6 hours). The crude mixture was concentrated under vacuum, water was added and the product was extracted three times with dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated under vacuum and the crude residue was purified by flash column chromatography (diethyl ether) to give 4,5-Dihydro-3H-2-benzazepine **176d**.



^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.28 (quint, 2H, H-10, *J* 6.5 Hz), 2.78 (t, 2H, H-9, *J* 6.5 Hz), 3.63 (td, 2H, H-11, *J* 6.5 Hz, *J* 1.5 Hz), 7.21-7.25 (m, 1H, H-7), 7.29-7.37 (m, 3H, H-4, H-5, H-6), 8.50 (br s, 1H, H-2). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 32.3 (C-10), 32.6 (C-9), 51.6 (C-11), 126.3 (C_{Ar}-H), 129.1 (C-7), 129.9 (C_{Ar}-H), 130.0 (C_{Ar}-H), 134.4 (C-3), 140.9 (C-8), 163.9 (C-2).

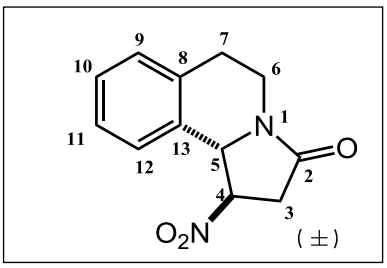
A.1.11. General procedure B for the synthesis of pyrrolidin-2-one 177a-d

A 5 mL one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl-3-nitropropanoate **169** (1.0 eq), cyclic imine **176a-d** (1.5 eq), benzoic acid **179** (1.5 eq) and toluene (0.04 mol/L). The reaction mixture was pumped/filled three times with N_2 and stirred at 70 ˚C until full consumption of methyl-3-nitropropanoate **169** (monitored by TLC). The reaction mixture was concentrated under vacuum and the residue taken up in dichloromethane, washed three times with 1M K_2CO_3 and purified by flash column chromatography

A.1.11.1. 1-Nitro-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one 177a

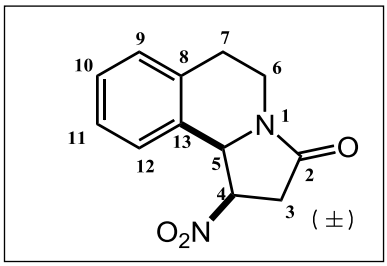
Prepared according to the general procedure **B** with 67.7 mg, (0.51 mmol) of methyl-3-nitropropanoate **169**. **177a** (110 mg, 95%, dr 2:1) was obtained as a separable mixture of two

diastereoisomers which were purified by flash column chromatography (diethyl ether, R_{fmajor} = 0.60, R_{fminor} = 0.05 in diethyl ether).



Major diastereoisomer isolated as a brown oil.

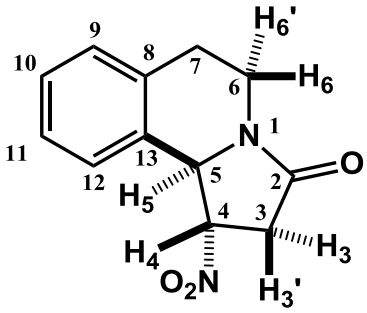
IR (cm^{-1}) ν_{max} 1702 (C=O), 1554 (NO_2), 1494 (C=C aromatic), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.78 (dd, 1H, H-7, *J* 16.5 Hz, *J* 2.2 Hz), 2.95-3.01 (m, 1H, H-7'), 3.03 (dd, 1H, H-3, *J* 17.5 Hz, *J* 10.0 Hz), 3.13-3.22 (m, 1H, H-6), 3.30 (ddd, 1H, H-3', *J* 17.5 Hz, *J* 7.0 Hz, *J* 1.0 Hz), 4.36 (ddd, 1H, H-6', *J* 13.0 Hz, *J* 6.5 Hz, *J* 2.0 Hz), 5.15 (ddd, 1H, H-4, *J* 10.0 Hz, *J* 7.0 Hz, *J* 5.5 Hz), 5.32 (d, 1H, H-5, *J* 5.5 Hz), 7.18 (d, 1H, H-9, J 6.5 Hz), 7.25-7.35 (m, 3H, H-10, H-11 and H-12). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 27.8 (C-7), 36.4 (C-3), 37.5 (C-6), 60.9 (C-5), 84.6 (C-4), 124.8 (C-12), 127.5 (C-11), 128.3 (C-10), 129.7 (C-9), 133.4 (C-13), 134.0 (C-8), 167.6 (C-2). ***m/z*** (ES-) 231 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2O_3Na^+$) requires ***m/z*** 255.0740, found ***m/z*** 255.0742.



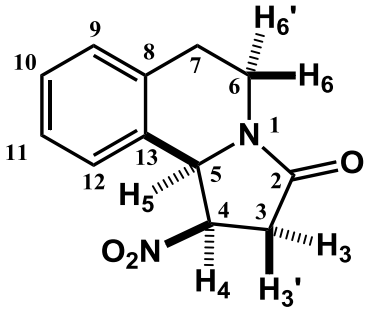
Minor diastereomer, isolated as a green oil.

IR (cm^{-1}) ν_{max} 1705 (C=O), 1552 (NO_2), 1495 (C=C aromatic), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.69-2.80 (m, 1H, H-7), 2.90-3.09 (m, 4H, H-7', H-3 and H-6), 4.45-4.52 (m, 1H, H-6'), 5.30 (d, 1H, H-5, *J* 6.0 Hz), 5.56 (t, 1H, H-4, *J* 6.0 Hz), 7.14-7.18 (m, 2H, H_{Ar}), 7.22-7.30 (m, 2H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 28.3 (C-7), 37.3 (C-3), 37.6 (C-6), 60.4 (C-5), 83.5 (C-4), 125.7 (C_{Ar}-H), 126.9 (C_{Ar}-H), 128.2 (C_{Ar}-H), 128.6 (C_{quat}), 129.7 (C_{Ar}-H), 135.5 (C_{quat}), 169.2 (C-2). ***m/z*** (ES-) 231 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2O_3Na^+$) requires ***m/z*** 255.0740, found ***m/z*** 255.0746.

nOe experiment on both diastereosiomers.



When H_4 was irradiated, we could see its interaction with H_5 and H_3'. When H_5 was irradiated, the interaction with H_4, H_3 and H_6' were seen. When irradiating H_6, the interaction with H_4 was observed but not with H_5. These suggested that H_4 and H_5 were on opposite side of the ring.

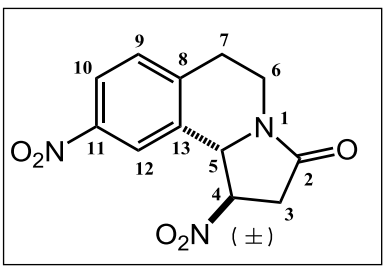


When H_6 was irradiated, interaction with $H_{3'}$ and $H_{6'}$ were observed. When $H_{6'}$ was irradiated, interaction with H_5, H_4 and $H_{3'}$ was seen. This result confirmed that in the case of the minor diastereoisomer H_4 and H_5 are on the same side of the molecule.

By combining the results of both nOe, the relative stereochemistry of the stereocenters 4 and 5 can be assigned as trans in the case of the major diastereoisomer and syn in the case of the minor diastereoisomer, as confirmed by X-ray crystallography on pyrrolidinones **172**.

A.1.11.2. 1,9-Dinitro-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one 177b

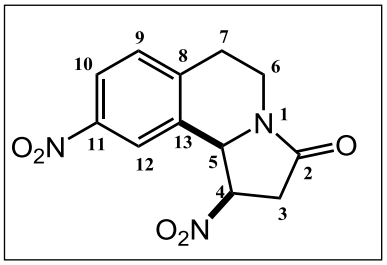
Prepared according to the general procedure **B** with 80.6 mg (0.60 mmol) of methyl-3-nitropropanoate **169**. **177b** (120 mg, 72%, dr 1:1) was obtained as a separable mixture of two diastereoisomers which were purified by flash column chromatography (1:1 dichloromethane / ethyl acetate; R_{fmajor} = 0.34, R_{fminor} = 0.11 in diethyl ether / ethyl acetate 5:2).



Major diastereoisomer isolated as a light brown solid.

mp 79-81 °C. **IR** (cm^{-1}) ν_{max} 1703 (C=O), 1588 (NO_2), 1557 (NO_2), 1348 (NO_2), 1347 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.92 (dd, 1H, H-7, *J* 17.0 Hz, *J* 2.5 Hz), 3.02-3.1 (m, 1H, H-7'), 3.07 (dd, 1H, H-3, *J* 18.0 Hz, *J* 10.0 Hz), 3.16-3.26 (m, 1H, H-6), 3.37 (ddd, 1H, H-3', *J* 18.0 Hz, *J* 6.5 Hz, *J* 1.0 Hz), 4.41 (ddd,

1H, H-6', *J* 13.0 Hz, *J* 6.5 Hz, *J* 2.0 Hz), 5.21 (ddd, 1H, H-4, *J* 10.0 Hz, *J* 6.5 Hz, *J* 5.0 Hz), 5.38 (d, 1H, H-5, *J* 5.0 Hz), 7.38 (d, 1H, H-9, *J* 8.5 Hz), 8.13 (dd, 1H, H-10, *J* 8.5 Hz, *J* 2.0 Hz), 8.24 (d, 1H, H-12, *J* 2.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 28.1 (C-7), 35.8 (C-3), 36.8 (C-6), 60.4 (C-5), 83.8 (C-4), 120.4 (C-12), 123.1 (C-10), 130.9 (C-9), 135.0 (C-13), 141.8 (C-8), 147.1 (C-11), 167.7 (C-2). ***m/z*** (ES-) 276 ($[M-H]^-$, 100%), HRMS (FI) exact mass calculated for $[M]^+$ ($C_{12}H_{11}N_3O_5$) requires ***m/z*** 277.0703, found ***m/z*** 277.0699.

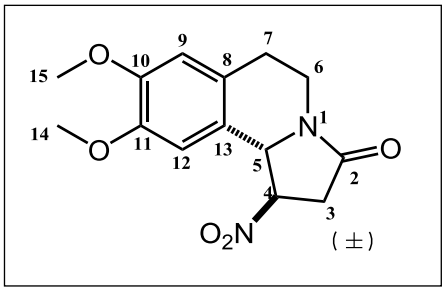


Minor diastereomer isolated as a brown oil.

IR (cm^{-1}) ν_{max} 1702 (C=O), 1590 (NO_2), 1554 (NO_2), 1348 (NO_2), 1347 (NO_2). **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 2.85-3.00 (m, 3H, H-7 and H-3), 3.06-3.014 (m, 1H, H-6), 3.23 (ddd, 1H, H-3', *J* 18.0 Hz, *J* 6.0 Hz, *J* 1.5 Hz), 4.43 (ddd, 1H, H-6', *J* 13.0 Hz, *J* 5.5 Hz, *J* 1.5 Hz), 5.56 (d, 1H, H-5, *J* 6.0 Hz), 5.93 (d, 1H, H-4, *J* 6.0 Hz), 7.47 (d, 1H, H-9, *J* 8.5 Hz), 8.13 (dd, 1H, H-10, *J* 8.5 Hz, *J* 2.0 Hz), 8.29 (d, 1H, H-12, *J* 2.0 Hz). **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 29.6 (C-7), 37.7 (C-3), 38.4 (C-6), 61.6 (C-5), 85.1 (C-4), 122.9 (C-12), 123.7 (C-10), 131.9 (C-9), 132.8 (C-13), 144.5 (C-8), 148.0 (C-11), 172.4 (C-2). ***m/z*** (ES-) 276 ($[M-H]^-$, 100%), HRMS (FI) exact mass calculated for $[M]^+$ ($C_{12}H_{11}N_3O_5$) requires ***m/z*** 277.0703, found ***m/z*** 277.0699.

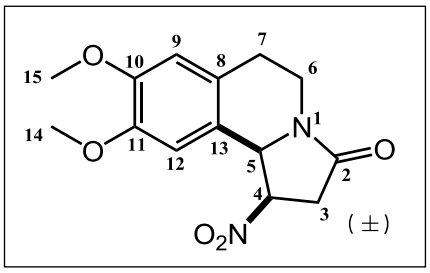
A.1.11.3. 8,9-Dimethoxy-1-nitro-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one 177c

Prepared according to the general procedure **B** with 1.0 g (7.3 mmol) of methyl-3-nitropropanoate **169**. **177c** (1.65 g, 77%, dr 4.5:1) was obtained as a separable mixture of two diastereoisomers which were purified by flash column chromatography (gradient from diethyl ether / ethyl acetate 2:1 to pure ethyl acetate; R_{f1} = 0.24, R_{f2} = 0.11 in diethyl ether / ethyl acetate 2:1).



Major diastereoisomer isolated as a yellowish solid.

mp 166-168 °C. **IR** (cm^{-1}) ν_{max} 1700 (C=O), 1612 (C=C aromatic), 1555 (NO_2), 1518 (C=C aromatic), 1362 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.67 (dd, 1H, H-7, *J* 16.0 Hz, *J* 4.0 Hz), 2.88-2.97 (m, 1H, H-7'), 3.03 (dd, 1H, H-3, *J* 17.5 Hz, *J* 9.5 Hz), 3.11 (td, 1H, H-6, *J* 13.0 Hz, *J* 4.0 Hz), 3.35 (ddd, 1H, H-3', *J* 17.5 Hz, *J* 7.0 Hz, *J* 1.0 Hz), 3.88 (s, 6H, H-14 and H-15), 4.41 (ddd, 1H, H-6', *J* 13.0 Hz, *J* 6.0 Hz, *J* 1.0 Hz), 5.12 (ddd, 1H, H-4, *J* 9.5 Hz, *J* 7.0 Hz, *J* 5.5 Hz), 5.24 (d, 1H, H-5, *J* 5.5 Hz), 6.62 (s, 1H, H-9), 6.75 (s, 1H, H-12). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 27.1 (C-7), 36.0 (C-3), 37.8 (C-6), 55.9 (C-14 or C-15), 56.0 (C-14 or C-15), 61.4 (C-5), 85.7 (C-4), 106.5 (C-12), 112.6 (C-9), 124.9 (C-13), 126.0 (C-8), 148.6 (C-10 or C-11), 148.9 (C-10 or C-11), 167.6 (C-2). ***m/z*** (ES-) 291 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2O_5Na^+$) requires ***m/z*** 315.0951, found ***m/z*** 315.0944.

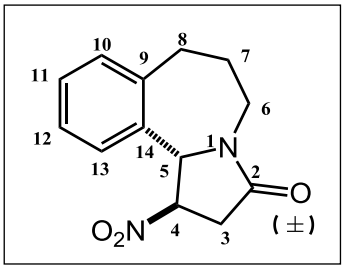


Minor diastereomer isolated as a green oil.

IR (cm^{-1}) ν_{max} 1701 (C=O), 1613 (C=C aromatic), 1554 (NO_2), 1517 (C=C aromatic), 1363 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.59 (dd, 1H, H-7, *J* 15.5 Hz, *J* 2.5 Hz), 2.76-2.86 (m, 1H, H-7'), 2.87-3.01 (m, 3H, H-3 and H-6), 3.80 (s, 3H, H-14 or H-15), 3.83 (s, 3H, H-15 or H-14), 4.40 (dd, 1H, H-6', *J* 13.0 Hz, *J* 4.5 Hz), 5.20 (d, 1H, H-5, *J* 6.0 Hz), 5.52 (t, 1H, H-4, *J* 6.0 Hz), 6.57 (s, 1H, H-9), 6.59 (s, 1H, H-12). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 27.8 (C-7), 37.2 (C-3), 37.4 (C-6), 55.8 (C-14 or C-15), 56.1 (C-15 or C-14), 60.3 (C-5), 83.5 (C-4), 108.5 (C-12), 111.9 (C-9), 120.1 (C-13), 127.9 (C-8), 147.9 (C-10 or C-11), 148.8 (C-11 or C-10), 169.2 (C-2). ***m/z*** (ES-) 291 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2O_5Na^+$) requires ***m/z*** 315.0951, found ***m/z*** 315.0943.

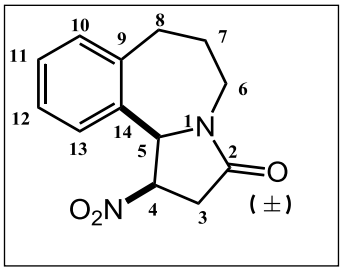
A.1.11.4. 1-Nitro-1,2,5,6,7,11b-hexahydro-3H-pyrrolo[2,1-a][2]benzazepin-3-one 177d

Prepared according to the general procedure **B** with 100 mg (0.75 mmol) of methyl-3-nitropropanoate **169**. **177d** (140 mg, 75%, dr 7:1) was obtained as a separable mixture of two diastereoisomers which were purified by flash column chromatography (dichloromethane / ethyl acetate 6:1, R_{f1} = 0.56, R_{f2} = 0.17).



Major diastereoisomer isolated as a light yellow solid.

IR (cm^{-1}) ν_{max} 1700 (C=O), 1555 (NO_2), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.75-1.87 (m, 1H, H-7), 2.02-2.14 (m, 1H, H-7'), 2.73 (dt, 1H, H-8, *J* 15.0 Hz, *J* 4.5 Hz), 2.85 (ddd, 1H, H-8', *J* 15.0 Hz, *J* 11.0 Hz, *J* 4.5 Hz), 2.95-3.00 (m, 1H, H-6), 3.01 (dd, 1H, H-3, *J* 17.5 Hz, *J* 8.0 Hz), 3.23 (dd, 1H, H-3', *J* 17.5 Hz, *J* 5.0 Hz), 4.21 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 7.5 Hz, *J* 3.0 Hz), 5.27 (dt, 1H, H-4, *J* 8.0 Hz, *J* 5.0 Hz), 5.35 (d, 1H, H-5, *J* 5.0 Hz), 7.17 (d, 2H, H-10 and H-13, *J* 7.0 Hz), 7.24-7.32 (m, 2H, H-11 and H-12). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.5 (C-7), 31.3 (C-8), 35.3 (C-3), 40.0 (C-6), 67.2 (C-5), 84.5 (C-4), 126.8 (C-13), 127.3 (C-11 or C-12), 129.2 (C-12 or C-11), 131.3 (C-10), 134.7 (C-14), 139.4 (C-9), 168.7 (C-2). ***m/z*** (ES+) 269 ($[M+23]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}N_2O_3Na^+$) requires ***m/z*** 269.0897, found ***m/z*** 269.0901.



Minor diastereomer was obtained as a 1:2 mixture of minor / major diastereomer.

IR (cm^{-1}) ν_{max} 1699 (C=O), 1555 (NO_2), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.68-1.75 (m, 1H, H-7), 2.25-2.34 (m, 1H, H-7'), 2.44 (ddd, 1H, H-8, *J* 14.5 Hz, *J* 5.0 Hz, *J* 1.5 Hz), 2.84-2.91 (m, 1H, H-6), 2.90-2.97 (m, 1H, H-3), 3.14-3.21 (m, 2H, H-3' and H-8'), 4.11-4.17 (m, 1H, H-6'), 5.31-5.35 (m, 1H, H-5), 5.42 (br t, 1H, H-4, *J* 7.5 Hz), 7.09-7.13 (m, 1H, H_{Ar}), 7.21-7.35 (m, 3H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.2 (C-7), 29.5 (C-8), 35.7 (C-3), 38.1 (C-6), 68.5 (C-5), 83.5 (C-4), 126.9 (C_{Ar}-H), 127.4 (C_{Ar}-H), 129.3 (C_{Ar}-H), 131.9 (C_{Ar}-H), 135.2 (C_{quat}), 139.5 (C_{quat}), 170.3 (C-2). ***m/z*** (ES+) 269 ($[M+23]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}N_2O_3Na^+$) requires ***m/z*** 269.0897, found ***m/z*** 269.0901.

In order to easily compare the relative stereochemistry of the various pyrrolidinones above, the values of the coupling constants between H_3/H_4 and H_4/H_5, are summarised in the following table.

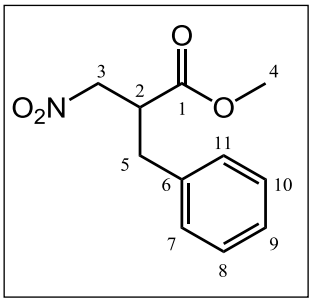
Compound	***J* H_3-H_4**	***J* $H_{3'}$-H_4**	***J* H_4-H_5**
172aa	9.0 Hz	2.0 Hz	2.0 Hz
172ab	9.0 Hz	2.0 Hz	2.0 Hz
172ac	8.5 Hz	2.0 Hz	2.0 Hz
172ad	9.0 Hz	2.0 Hz	2.0 Hz
172ae	8.5 Hz	1.5 Hz	1.5 Hz
172af	9.0 Hz	1.5 Hz	2.0 Hz
172ag	8.5 Hz	2.0 Hz	2.0 Hz
172ah	9.0 Hz	2.0 Hz	2.0 Hz
172ai	8.5 Hz	2.0 Hz	2.0 Hz
172aj	8.5 Hz	1.5 Hz	1.5 Hz
172ak	8.5 Hz	2.0 Hz	2.0 Hz
172al	8.5 Hz	2.0 Hz	2.0 Hz
172am	8.0 Hz	1.0 Hz	2.0 Hz
172ba	8.0 Hz	2.5 Hz	2.5 Hz
172ca	8.5 Hz	1.5 Hz	1.5 Hz
	9.0 Hz	2.0 Hz	2.0 Hz
172da	8.0 Hz	1.0 Hz	<1.0 Hz
	8.5 Hz	1.0 Hz	<1.0 Hz
172ea	8.0 Hz	2.5 Hz	2.5 Hz
172fa	multiplet	multiplet	2.5 Hz
172ga	8.0 Hz	2.5 Hz	2.5 Hz
172ha	8.5 Hz	2.5 Hz	2.5 Hz
172ia	7.0 Hz	4.5 Hz	2.0 Hz
172ja	8.5 Hz	multiplet	
172ka	8.5 Hz	3.5 Hz	3.5 Hz
172la	8.0 Hz	2.5 Hz	2.5 Hz
172ma	8.0 Hz	2.5 Hz	2.5 Hz
172na	8.0 Hz	2.5 Hz	2.5 Hz
172oa	8.5 Hz	2.5 Hz	2.5 Hz
172pa	8.5 Hz	2.5 Hz	2.5 Hz
172qa	8.5 Hz	2.5 Hz	2.5 Hz

Compound	diastereoisomer	*J* H_3-H_4	*J* $H_{3'}$-H_4	*J* H_4-H_5
177a	major	10.0 Hz	7.0 Hz	5.5 Hz
	minor		6.0 Hz	6.0 Hz
177b	major	10.0 Hz	6.0 Hz	5.0 Hz
	minor			6.0 Hz
177c	major	9.0 Hz	7.0 Hz	5.5 Hz
	minor		6.0 Hz	6.0 Hz
177d	major	8.0 Hz	5.0 Hz	5.0 Hz
	minor			7.5 Hz

A.2 Experimental- Chapter 2

Compounds **194a-d** were synthesized according to a modified of literature procedures.[1]

A.2.1. Methyl 2-benzyl-3-nitropropanoate 194a

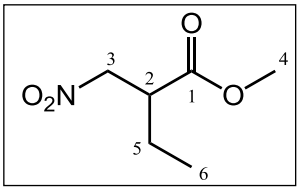


A 250 mL, flame dried, nitrogen purged, one-necked flask, equipped with a magnetic stirrer bar and a nitrogen balloon, was charged with dry tetrahydrofuran (75 mL) and diisopropylamine (6.9 mL, 49.5 mmol, 2.2 eq). The mixture was cooled to -10 ˚C, and *n*-butyllithium (2.5 M in hexanes, 18.0 mL, 45.0 mmol, 2.0 eq) was added dropwise. The mixture was stirred at 0 ˚C for 30 min, then cooled to -78 ˚C and a solution of methyl 3-nitropropanoate (3.0 g, 22.5 mmol, 1.0 eq) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (27.2 mL, 225.0 mmol, 10.0 eq) in dry tetrahydrofuran (20 mL) was added dropwise. The reaction was stirred for 30 min at -78 ˚C, then benzyl bromide (2.6 mL, 22.5 mmol, 1.0 eq) was added dropwise. The conversion was monitored by TLC (petroleum ether/ethyl acetate 9:1). After 2 hours, TLC and ^{1}H NMR showed full conversion of the starting material. The reaction was quenched with 1M HCl and extracted three times with ethyl acetate. The organic layer was washed once with water then once with a saturated aqueous solution of sodium bicarbonate. It was dried over anhydrous Na_2SO_4,

filtered and the filtrate was concentrated under vacuum. The purification was achieved by flash column chromatography (gradient from petroleum ether/ethyl acetate 95:5 to 90:10) to give 3.7 g (73 % yield) of the desired product **194a** as a light yellow oil.

IR (cm^{-1}) ν_{max} 1737 (C=O), 1605 (C=C aromatic), 1557 (NO_2), 1497 (C=C aromatic), 1379 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.84 (dd, 1H, H-5, *J* 14.0 Hz, *J* 9.0 Hz), 3.15 (dd, 1H, H-5', *J* 14.0 Hz, *J* 6.0 Hz), 3.43-3.53 (m, 1H, H-2), 3.74 (s, 3H, H-4), 4.37 (dd, 1H, H-3, *J* 14.5 Hz, *J* 4.5 Hz), 4.67 (dd, 1H, H-3', *J* 14.5 Hz, *J* 9.0 Hz), 7.16 (br d, 2H, H-7 and H-11, *J* 7.0 Hz), 7.26-7.31 (m, 1H, H-9), 7.31-7.37 (m, 2H, H-8 and H-10). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 35.1 (C-5), 44.5 (C-2), 52.4 (C-4), 74.0 (C-3), 127.4 (C-9), 128.8 (2x C_{Ar}-H), 129.0 (2x C_{Ar}-H), 136.4 (C-6), 172.0 (C-1). ***m/z*** (ES+) 246 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{13}NO_4Na^+$) requires ***m/z*** 246.0737, found ***m/z*** 246.0736.

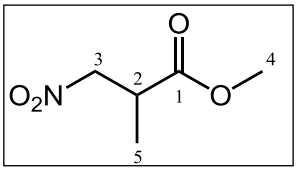
A.2.2. Methyl 2-ethyl-3-nitropropanoate 194b



A 250 mL, flame dried, nitrogen purged, one-necked flask, equipped with a magnetic stirrer bar and a nitrogen balloon, was charged with dry tetrahydrofuran (50 mL) and diisopropylamine (4.6 mL, 33.0 mmol, 2.2 eq). The mixture was cooled to -10 °C, and then *n*-butyllithium (1.6 M in hexanes, 18.8 mL, 30.0 mmol, 2.0 eq) was added dropwise. The mixture was stirred at 0 °C for 30 min. It was then cooled to -78 °C and a solution of methyl 3-nitropropanoate (2.0 g, 15.0 mmol, 1.0 eq) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (18.1 mL, 150.0 mmol, 10.0 eq) in dry tetrahydrofuran (10 mL) was added dropwise. The reaction was stirred for 30 min at -78 °C followed by the slow addition of ethyl iodide (1.8 mL, 22.5 mmol, 1.5 eq). The reaction was allowed to warm up to room temperature overnight, and then it was quenched with 1 M HCl, extracted three times with diethyl ether. The organic layer was washed once with water and once with a saturated aqueous solution of sodium bicarbonate. It was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The purification was achieved by flash column chromatography (petroleum ether / diethyl ether 6:1, R_f = 0.38) to give 0.8 g (38 % yield) of the desired product **194b** as a light yellow oil.

IR (cm^{-1}) ν_{max} 1737 (C=O), 1558 (NO_2), 1380 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.98 (t, 3H, H-6, *J* 7.5 Hz), 1.56-1.88 (m, 2H, H-5), 3.06-3.31 (m, 1H, H-2), 3.75 (s, 3H, H-4), 4.43 (dd, 1H, H-3, *J* 14.0 Hz, *J* 5.0 Hz), 4.75 (dd, 1H, H-3', *J* 14.0 Hz, *J* 9.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 11.0 (C-6), 22.5 (C-5), 44.1 (C-2), 52.3 (C-4), 74.8 (C-3), 172.6 (C-1). ***m/z*** HRMS (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_6H_{15}N_2O_4^+$) requires ***m/z*** 179.1032, found ***m/z*** 179.1038.

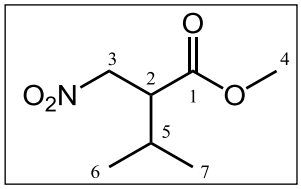
A.2.3. Methyl 2-methyl-3-nitropropanoate 194c



A 250 mL, flame dried, nitrogen purged, one-necked flask, equipped with a magnetic stirrer bar and a nitrogen balloon, was charged with dry tetrahydrofuran (50 mL) and diisopropylamine (4.6 mL, 33.0 mmol, 2.2 eq). The mixture was cooled to -10 °C, and then *n*-butyllithium (1.6 M in hexanes, 18.8 mL, 30.0 mmol, 2.0 eq) was added dropwise. The mixture was stirred at 0 °C for 30 min. It was then cooled to -78 °C and a solution of methyl 3-nitropropanoate (2.0 g, 15.0 mmol, 1.0 eq) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (18.1 mL, 150.0 mmol, 10.0 eq) in dry tetrahydrofuran (10 mL) was added dropwise. The reaction was stirred for 30 min at -78 °C followed by the slow addition of methyl iodide (1.4 mL, 22.5 mmol, 1.5 eq). The reaction was allowed to warm up to room temperature overnight. It was quenched with 1 M HCl, and then extracted three times with diethyl ether. The organic layer was washed once with water and once with a saturated aqueous solution of sodium bicarbonate. It was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The purification was achieved by flash column chromatography (petroleum ether/diethyl ether 6:1, R_f = 0.43) to give 0.9 g (45 % yield) of the desired product **194c** as a light yellow oil.

IR (cm^{-1}) ν_{max} 1737 (C=O), 1557 (NO_2), 1381 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.29 (d, 3H, H-5, *J* 7.5 Hz), 3.15-3.36 (m, 1H, H-2), 3.75 (s, 3H, H-4), 4.41 (dd, 1H, H-3, *J* 14.0 Hz, *J* 5.5 Hz), 4.73 (dd, 1H, H-3', *J* 14.0 Hz, *J* 8.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.3 (C-5), 37.5 (C-2), 52.5 (C-4), 76.3 (C-3), 172.9 (C-1). ***m/z*** (ES+) HRMS (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_5H_{13}N_2O_4^+$) requires ***m/z*** 165.0875, found ***m/z*** 165.0873.

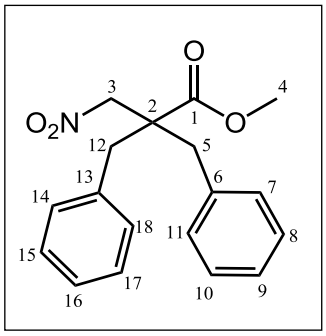
A.2.4. Methyl 3-methyl-2-(nitromethyl)butanoate 194d



A 250 mL, flame dried, nitrogen purged, one-necked flask, equipped with a magnetic stirrer bar and a nitrogen balloon, was charged with dry tetrahydrofuran (66 mL), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (13.0 mL) and diisopropylamine (4.6 mL, 33.0 mmol, 2.2 eq). The mixture was cooled to -10 °C, and then *n*-butyllithium (1.6 M in hexanes, 18.8 mL, 30.0 mmol, 2.0 eq) was added dropwise. The mixture was stirred at 0 °C for 30 min. It was then cooled to -78 °C and a solution of methyl 3-nitropropanoate (2.0 g, 15.0 mmol, 1.0 eq) in dry tetrahydrofuran (10 mL) was added dropwise. The reaction was stirred for 30 min followed by the slow addition of isopropyliodide (1.8 mL, 22.5 mmol, 1.5 eq). The reaction was allowed to warm up to -25 °C over 4 hours and then warmed up to room temperature. The reaction was quenched with glacial acetic acid (5 mL), stirred for 5 min, then water (5 mL) was added and reaction allowed to warm up to room temperature. The product was extracted 3 times with diethyl ether. The organic layer was washed once with water and once with a saturated aqueous solution of sodium bicarbonate. It was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The purification was achieved by flash column chromatography (petroleum ether/diethyl ether 4:1, R_f = 0.69) to give 1.6 g (58 % yield) of desired product **194d** as a light yellow oil.

IR (cm^{-1}) ν_{max} 1733 (C=O), 1556 (NO_2), 1377 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.98 (d, 3H, H-6 or H-7, *J* 5.5 Hz), 0.99 (d, 3H, H-7 or H-6, *J* 5.5 Hz), 2.02-2.12 (m, 1H, H-5), 3.12 (ddd, 1H, H-2, *J* 10.5 Hz, *J* 5.5 Hz, *J* 4.0 Hz), 3.74 (s, 3H, H-4), 4.42 (dd, 1H, H-3, *J* 14.5 Hz, *J* 4.0 Hz), 4.79 (dd, 1H, H-3', *J* 14.5 Hz, *J* 10.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 19.7 (C-6 and C-7), 28.8 (C-5), 48.9 (C-2), 52.2 (C-4), 73.7 (C-3), 172.3 (C-1). ***m/z*** (ES+) 198 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{13}NO_4Na^+$) requires ***m/z*** 198.0737, found ***m/z*** 198.0740.

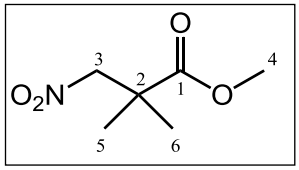
A.2.5. Methyl 2,2-dibenzyl-3-nitropropanoate 195a



When the reaction for the synthesis of the nitroester **194a** was allowed to stir overnight, 10-20% of the bis-substituted product **195a** was isolated as a light yellow oil.

IR (cm^{-1}) ν_{max} 1735 (C=O), 1603 (C=C aromatic), 1554 (NO_2), 1495 (C=C aromatic), 1377 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.15 (d, 2H, H-5 or H-12, *J* 14.0 Hz), 3.34 (d, 2H, H-12 or H-5, *J* 14.0 Hz), 3.65 (s, 3H, H-4), 4.43 (s, 2H, H-3), 7.14 (br d, 4H, H-7, H-11, H-14 and H-18, *J* 6.5 Hz), 7.25-7.39 (m, 6H, H-8, H-9, H-10, H-15, H-16 and H-17). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 40.7 (C-5 and C-12), 51.8 (C-2 or C-4), 52.1 (C-4 or C-2), 74.7 (C-3), 127.5 (C-9 and C-16), 128.7 (C-8, C-10, C-15 and C-17), 130.1 (C-7, C-11, C-14 and C-18), 135.3 (C-6 and C-13), 172.7 (C-1). ***m/z*** (ES+) 336 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{19}NO_4Na^+$) requires ***m/z*** 336.1206, found ***m/z*** 336.1201.

A.2.6. Methyl 2-dimethyl-3-nitropropanoate 195c



When the reaction for the synthesis of the nitroester **194c** was allowed to stir overnight, 10-20% of the bis-substituted product **195c** was isolated as a light yellow oil.

IR (cm^{-1}) ν_{max} 1735 (C=O), 1558 (NO_2), 1376 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.31 (s, 6H, H-5 and H-6), 3.75 (s, 3H, H-4), 4.56 (s, 2H, H-3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 23.4 (C-5 and C-6), 42.7 (C-2), 53.1 (C-4), 82.7 (C-3), 175.1 (C-1). ***m/z*** HRMS (ES+) exact mass calculated for $[M+NH_4]^+$ ($C_6H_{15}N_2O_4^+$) requires ***m/z*** 179.1032, found ***m/z*** 179.1025.

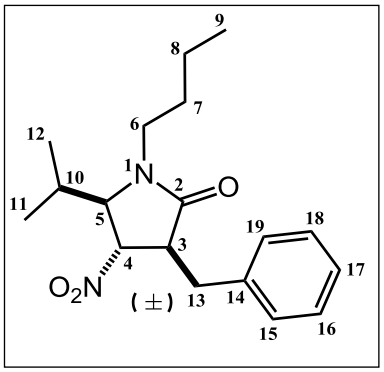
A.2.7. General procedure C for the synthesis of nitropyrrolidinon-2-ones 193

A 5 mL round-bottom flask, equipped with a rubber seal and a magnetic stirrer bar was charged with the corresponding substituted methyl 3-nitropropanoate **194a-d** (100 mg, 1.0 eq), benzoic acid **179** (1.5 eq) and toluene (3 mL). The reaction mixture was pumped/filled three times with N_2. Then the corresponding amine (1.5 eq) and aldehyde (1.5 eq) were added *via* a microsyringe. The reaction was

stirred at 70 °C under N_2 atmosphere and the conversion was monitored by TLC. Upon completion, usually from 6 to 12 hours, the reaction mixture was concentrated under vacuum. The residue was dissolved in dichloromethane, washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography.

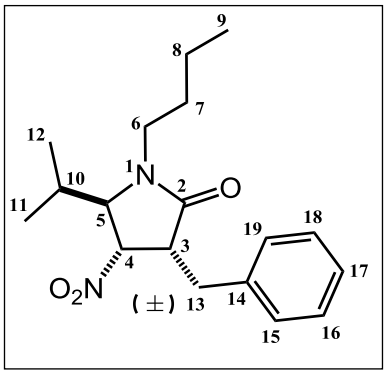
A.2.7.1. 3-Benzyl-1-butyl-5-isopropyl-4-nitropyrrolidin-2-one 193aaa

Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, butylamine **167a** and isobutyraldehyde **166a**. **193aaa** (100 mg, 70% yield) was obtained as a separable mixture of two diastereoisomers (dr 4:1) which were isolated by flash column chromatography (petroleum ether / diethyl ether 3:1, R_{fmajor} = 0.22 and R_{fminor} = 0.08).



Major diastereoisomer (56% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1699 (C=O), 1604 (C=C aromatic), 1557 (NO_2), 1497 (C=C aromatic), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.30 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.85 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 0.95 (t, 3H, H-9, *J* 7.5 Hz), 1.23-1.41 (m, 2H, H-8), 1.42-1.61 (m, 2H, H-7), 2.03-2.14 (m, 1H, H-10), 2.74 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.12 (dd, 1H, H-13, *J* 14.5 Hz, *J* 6.0 Hz), 3.17 (dd, 1H, H-13', *J* 14.5 Hz, *J* 6.0 Hz), 3.38 (q, 1H, H-3, *J* 6.0 Hz), 3.82 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.99 (dd, 1H, H-5, *J* 5.5 Hz, *J* 4.0 Hz), 4.61 (dd, 1H, H-4, *J* 6.0 Hz, *J* 5.5 Hz), 7.21-7.26 (m, 3H, H-15, H-17 and H-19), 7.28-7.35 (m, 2H, H-16 and H-18). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9 or C-11), 13.8 (C-11 or C-9), 17.5 (C-12), 19.9 (C-8), 27.0 (C-10), 28.6 (C-7), 33.8 (C-13), 40.1 (C-6), 49.5 (C-3), 63.6 (C-5), 81.6 (C-4), 127.2 (C-17), 128.9 (C16 and C-18), 129.7 (C-15 and C-19), 136.3 (C-14), 170.4 (C-2). ***m/z*** (ES+) 319 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2O_3Na^+$) requires ***m/z*** 341.1836, found ***m/z*** 341.1832.

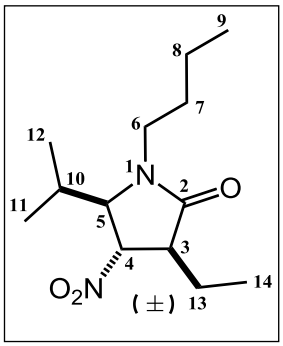


Minor diastereoisomer (14% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1698 (C=O), 1604 (C=C aromatic), 1556 (NO_2), 1497 (C=C aromatic), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.79 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.97 (t, 3H, H-9, *J* 7.5 Hz), 1.03 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 1.35-1.47 (m, 2H, H-8), 1.51-1.62 (m, 2H, H-7), 2.08-2.20 (m, 1H, H-10), 2.54 (dd, 1H, H-13, *J* 15.0 Hz, *J* 11.0 Hz), 2.96 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.5 Hz), 3.07 (ddd, 1H, H-3, *J* 11.0 Hz, *J* 7.5 Hz, *J* 4.0 Hz), 3.47 (dd, 1H, H-13', *J* 15.0 Hz, *J* 4.0 Hz), 3.75 (d, 1H, H-5, *J* 4.0 Hz), 3.76-3.82 (m, 1H, H-6'), 4.88 (d, 1H, H-4, *J* 7.5 Hz), 7.17 (br d, 2H, H_{Ar}, *J* 7.5 Hz), 7.22-7.27 (m, 1H, H-17), 7-29-7.34 (m, 2H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 15.8 (C-11 or C-12), 18.5 (C-12 or C-11), 22.6 (C-8), 28.4 (C-10), 28.8 (C-7), 31.6 (C-13), 41.0 (C-6), 47.3 (C-3), 66.4 (C-5), 82.9 (C-4), 126.8 (C-17), 128.6 (2x C_{Ar}-H), 128.7 (2x C_{Ar}-H), 138.0 (C-14), 171.2 (C-2). ***m/z*** (ES-) 317 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2O_3Na^+$) requires ***m/z*** 341.1836, found ***m/z*** 341.1830.

A.2.7.2. 1-Butyl-3-ethyl-5-isopropyl-4-nitropyrrolidin-2-one 193aab

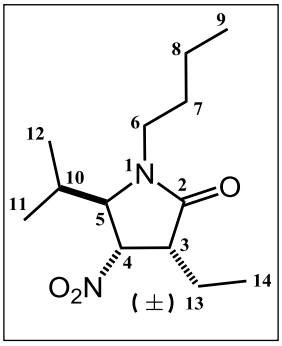
Prepared according to the general procedure **C** with methyl 2-ethyl-3-nitropropanoate **194b**, butylamine **167a** and isobutyraldehyde **166a**. **193aab** (100 mg, 76% yield) was obtained as a separable mixture of two diastereoisomers (dr 5.5:1) which were isolated by flash column chromatography (gradient from petroleum ether / ethyl acetate 8:1 to 1:1, R_{fmajor} = 0.20 and R_{fminor} = 0.07 in petroleum ether /ethyl acetate 8:1).



Major diastereoisomer (63% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1697 (C=O), 1557 (NO_2), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.94 (t, 3H, H-9, *J* 7.5 Hz), 1.00 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 1.03 (t, 3H, H-14, *J* 7.5 Hz), 1.26-1.40 (m, 2H, H-8), 1.44-1.63 (m, 3H, H-7 and H-13), 2.00 (dqd, 1H, H-13', *J* 14.5 Hz, *J* 7.5 Hz, *J* 5.0 Hz), 2.18-2.27 (m, 1H, H-10), 2.78 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 2.94 (dt, 1H, H-3, *J* 9.0 Hz, *J* 5.0 Hz), 3.81 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.02 (t, 1H, H-5, *J* 5.0 Hz), 4.61 (t, 1H, H-4, *J* 5.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 11.0 (C-14), 13.7 (C-9), 14.7 (C-11 or C-12), 17.6 (C-12 or C-11), 19.9

(C-8), 22.8 (C-13), 27.2 (C-10), 28.6 (C-7), 40.0 (C-6), 49.7 (C-3), 64.3 (C-5), 83.8 (C-4), 171.4 (C-2). ***m/z*** (ES-) 255 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{13}H_{24}N_2O_3Na^+$) requires ***m/z*** 279.1679, found ***m/z*** 279.1680.

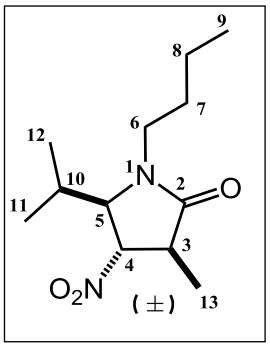


Minor diastereoisomer (13% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1695 (C=O), 1556 (NO_2), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.82 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.94 (t, 3H, H-9, *J* 7.5 Hz), 1.03-1.12 (m, 6H, H-12 or H-11 and H-14), 1.26-1.45 (m, 3H, H-8 and H-13), 1.47-1.63 (m, 2H, H-7), 1.92-2.05 (m, 1H, H-13'), 2.11-2.20 (m, 1H, H-10), 2.65 (td, 1H, H-3, *J* 8.5 Hz, *J* 5.0 Hz), 2.90 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.68-3.78 (m, 1H, H-6'), 3.83 (d, 1H, H-5, *J* 4.0 Hz), 5.06 (d, 1H, H-4, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 12.5 (C-14), 13.7 (C-9), 15.7 (C-11 or C-12), 18.5 (C-12 or C-11), 19.3 (C-13), 20.0 (C-8), 28.2 (C-10), 28.8 (C-7), 40.7 (C-6), 47.1 (C-3), 65.6 (C-5), 83.3 (C-4), 171.8 (C-2). ***m/z*** (ES-) 255 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{13}H_{24}N_2O_3Na^+$) requires ***m/z*** 279.1679, found ***m/z*** 279.1681.

A.2.7.3. 1-Butyl-5-isopropyl-3-methyl-4-nitropyrrolidin-2-one 193aac

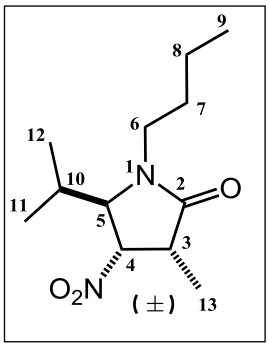
Prepared according to the general procedure **C** with methyl 2-methyl-3-nitropropanoate **194c**, butylamine **167a** and isobutyraldehyde **166a**. **193aac** (100 mg, 71% yield) was obtained as a separable mixture of two diastereoisomers (dr 3.5:1) which were isolated by flash column chromatography (petroleum ether / ethyl acetate 6:1, R_{fmajor} = 0.68 and R_{fminor} = 0.56).



Major diastereoisomer (55% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1698 (C=O), 1557 (NO_2), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.93 (t, 3H, H-9, *J* 7.5 Hz), 0.99 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 1.26-1.40 (m, 2H, H-8), 1.37 (d, 3H, H-13, *J* 7.5 Hz), 1.43-1.58 (m, 2H, H-7), 2.22 (septd, 1H, H-10, *J* 7.0 Hz, *J* 5.0 Hz), 2.77 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.04 (m, 1H, H-3), 3.81 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.05 (t, 1H, H-5, *J* 5.0 Hz), 4.50 (t, 1H, H-4, *J* 5.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 14.7 (C-11 or C-12), 15.0 (C-13), 17.6 (C-12 or C-11), 19.9 (C-8), 27.0 (C-10), 28.6 (C-7), 39.6 (C-6), 43.1 (C-3), 63.9 (C-

5), 85.7 (C-4), 171.9 (C-2). ***m/z*** (ES-) 241 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{12}H_{22}N_2O_3Na^+$) requires ***m/z*** 265.1523, found ***m/z*** 265.1518.

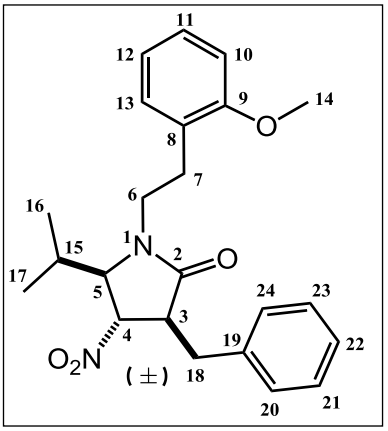


Minor diastereoisomer (16% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1696 (C=O), 1556 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.79 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.93 (t, 3H, H-9, *J* 7.5 Hz), 1.04 (d, 3H, H-12 or H-11, *J* 7.0 Hz) , 1.16 (d, 3H, H-13, *J* 7.5 Hz), 1.28-1.44 (m, 2H, H-8) , 1.47-1.63 (m, 2H, H-7), 2.11-2.19 (m, 1H, H-10), 2.83-2.95 (m, 2H, H-6 and H-3), 3.74 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.93 (d, 1H, H-5, *J* 3.0 Hz), 4.98 (d, 1H, H-4, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 10.2 (C-13), 13.7 (C-9), 15.4 (C-11 or C-12), 18.4 (C-12 or C-11), 19.9 (C-8), 27.8 (C-10), 28.7 (C-7), 39.9 (C-3), 40.6 (C-6), 64.9 (C-5), 83.9 (C-4), 172.1 (C-2). ***m/z*** (ES-) 241 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{12}H_{22}N_2O_3Na^+$) requires ***m/z*** 265.1523, found ***m/z*** 265.1525.

A.2.7.4. 3-Benzyl-5-isopropyl-1-[2-(2-methoxyphenyl)ethyl]-4-nitropyrrolidin-2-one 193afa

Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, 2-(2-methoxyphenyl)ethanamine **167f** and isobutyraldehyde **166a**. **193afa** (106 mg, 60% yield) was obtained as a separable mixture of two diastereoisomers (dr 4:1) which were isolated by flash column chromatography (petroleum ether / diethyl ether 1:1, R_{fmajor} = 0.18 and R_{fminor} = 0.13).

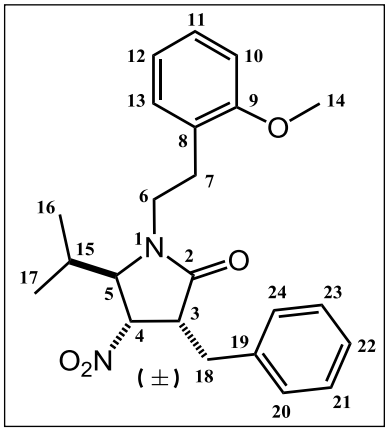


Major diastereoisomer (48% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1699 (C=O), 1602 (C=C aromatic), 1588 (C=C aromatic), 1557 (NO_2), 1495 (C=C aromatic), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.27 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 0.79 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 2.05-2.15 (m, 1H, H-15), 2.74-2.85 (m, 1H, H-7), 2.92-3.01 (m, 2H, H-7' and H-6), 3.08 (dd, 1H, H-18, *J* 14.0 Hz, *J* 5.5 Hz), 3.16 (dd, 1H, H-18', *J* 14.0 Hz, *J* 6.5 Hz), 3.29 (m, 1H, H-3), 3.84 (s, 3H, H-14), 3.89 (dd, 1H, H-5, *J* 6.0 Hz, *J* 3.5 Hz), 4.03-4.11 (m, 1H, H-6'), 4.55 (dd, 1H, H-

4, *J* 7.0 Hz, *J* 6.0 Hz), 6.86 (br d, 1H, H-10, *J* 8.0 Hz), 6.91 (br t, 1H, H-12, *J* 7.5 Hz), 7.17 (dd, 1H, H-13, *J* 7.5 Hz, *J* 1.5 Hz), 7.20-7.26 (m, 4H, H-11, H-20, H-22 and H-24), 7.27-7.33 (m, 2H, H-21 and H-23). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 (C-16 or C-17), 17.4 (C-17 or C-16), 26.8 (C-15), 27.8 (C-7), 33.6 (C-18), 40.1 (C-6), 49.2 (C-3), 55.2 (C-14), 63.7 (C-5), 81.6 (C-4), 110.3 (C-10), 120.7 (C-12), 126.4 (C-8), 127.2 (C-22), 128.2 (C-11), 128.8 (C-21 and C-23), 129.7 (C-20 and C-24), 130.6 (C-13), 136.4 (C-19), 157.5 (C-9), 170.4 (C-2). ***m/z*** (ES-) 395 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{29}N_2O_4^+$) requires ***m/z*** 397.2122, found ***m/z*** 397.2122.

Minor diastereoisomer (12% yield, isolated as a light yellow oil).

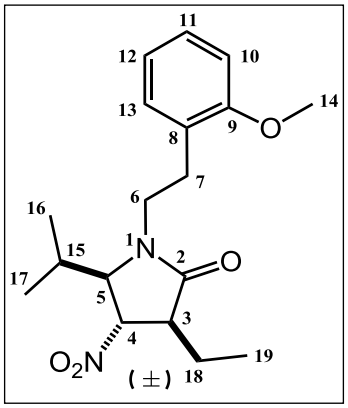


IR (cm^{-1}) ν_{max} 1700 (C=O), 1602 (C=C aromatic), 1588 (C=C aromatic), 1556 (NO_2), 1495 (C=C aromatic), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.77 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 0.99 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 2.09-2.17 (m, 1H, H-15), 2.56 (dd, 1H, H-18, *J* 15.0 Hz, *J* 11.0 Hz), 2.85-2.93 (m, 1H, H-7), 2.95-3.02 (m, 1H, H-7'), 3.06 (ddd, 1H, H-3, *J* 11.0 Hz, *J* 7.5 Hz, *J* 4.0 Hz), 3.24 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 9.5 Hz, *J* 5.5 Hz), 3.46 (dd, 1H, H-18', *J* 15.0 Hz, *J* 4.0 Hz), 3.75 (br d, 1H, H-5, *J* 4.0 Hz), 3.85 (s, 3H, H-14), 3.95 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 9.5 Hz, *J* 6.0 Hz), 4.85 (d, 1H, H-4, *J* 7.5 Hz), 6.86 (br d, 1H, H-10, *J* 8.0 Hz), 6.92 (br t, 1H, H-12, *J* 7.5 Hz), 7.17 (br d, 2H, $H_{Ar\text{-}benzyl}$, *J* 7.5 Hz), 7.20-7.27 (m, 3H, H-11, H-13 and H-22), 7.29-7.34 (m, 2H, $H_{Ar\text{-}benzyl}$). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 16.0 (C-16 or C-17), 18.5 (C-17 or C-16), 28.4 (C-7), 28.5 (C-15), 31.6 (C-18), 41.2 (C-6), 47.1 (C-3), 55.2 (C-14), 66.6 (C-5), 82.9 (C-4), 110.2 (C-10), 120.7 (C-12), 126.6 (C-8), 126.8 (C-22), 128.0 (C-11), 128.6 (2x C_{Ar}-H), 128.7 (2x C_{Ar}-H), 130.7 (C-13), 138.2 (C-19), 157.3 (C-9), 171.3 (C-2). ***m/z*** (ES-) 395 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{28}N_2O_4Na^+$) requires ***m/z*** 419.1941, found ***m/z*** 419.1937.

A.2.7.5. 3-Ethyl-5-isopropyl-1-[2-(2-methoxyphenyl)ethyl]-4-nitropyrrolidin-2-one 193afb

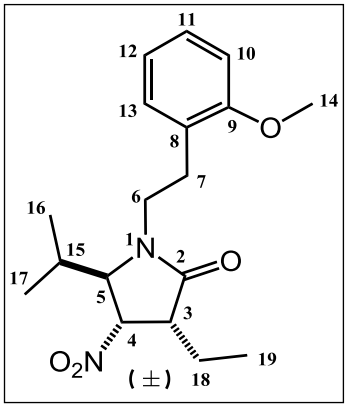
Prepared according to the general procedure **C** with methyl 2-methyl-3-nitropropanoate **194b**, 2-(2-methoxyphenyl)ethanamine **167f** and isobutyraldehyde **166a**. **193afb** (106 mg, 71% yield) was

obtained as a separable mixture of two diastereoisomers (dr 5:1) which were isolated by flash column chromatography (petroleum ether / diethyl ether 2:1, R_{fmajor} = 0.25 and R_{fminor} = 0.16).



Major diastereoisomer (58% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1698 (C=O), 1602 (C=C aromatic), 1588 (C=C aromatic), 1557 (NO_2), 1495 (C=C aromatic), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.76 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 0.94 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 1.01 (t, 3H, H-19, *J* 7.5 Hz), 1.52-1.64 (m, 1H, H-18), 1.91-2.05 (m, 1H, H-18'), 2.18-2.31 (m, 1H, H-15), 2.80 (dt, 1H, H-7, *J* 13.5 Hz, *J* 6.5 Hz), 2.90 (ddd, 1H, H-3, *J* 9.0 Hz, *J* 6.5 Hz, *J* 5.0 Hz), 2.93-3.08 (m, 2H, H-6 and H-7'), 3.84 (s, 3H, H-14), 3.91 (dd, 1H, H-5, *J* 5.0 Hz, *J* 3.5 Hz), 4.04 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 7.5 Hz, *J* 6.5 Hz), 4.56 (br t, 1H, H-4, *J* 5.0 Hz), 6.85 (br d, 1H, H-10, *J* 7.5 Hz), 6.90 (br t, 1H, H-12, *J* 7.5 Hz), 7.17 (dd, 1H, H-13, *J* 7.5 Hz, *J* 1.5 Hz), 7.22 (td, 1H, H-11, *J* 7.5 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 10.9 (C-19), 14.7 (C-16 or C-17), 17.6 (C-17 or C-16), 22.7 (C-18), 27.0 (C-15), 28.0 (C-7), 40.1 (C-6), 49.3 (C-3), 55.2 (C-14), 64.5 (C-5), 83.9 (C-4), 110.2 (C-10), 120.7 (C-12), 126.5 (C-8), 128.1 (C-11), 130.6 (C-13), 157.5 (C-9), 171.3 (C-2). ***m/z*** (ES-) 333 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2O_4^+$) requires ***m/z*** 335.1965, found ***m/z*** 335.1965.



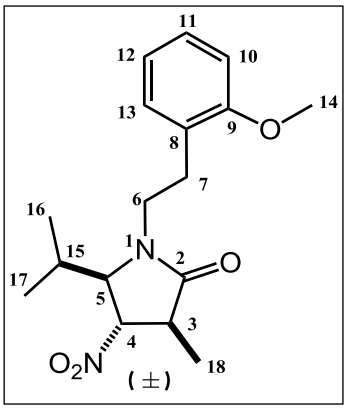
Minor diastereoisomer (13% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1696 (C=O), 1602 (C=C aromatic), 1588 (C=C aromatic), 1555 (NO_2), 1494 (C=C aromatic), 1371 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.81 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 1.03 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 1.06 (t, 3H, H-19, *J* 7.5 Hz), 1.28-1.39 (m, 1H, H-18), 1.96 (dqd, 1H, H-18', *J* 14.5 Hz, *J* 7.5 Hz, *J* 5.5 Hz), 2.11-2.21 (m, 1H, H-15), 2.66 (td, 1H, H-3, *J* 8.5 Hz, *J* 5.5 Hz), 2.85 (ddd, 1H, H-7, *J* 13.0 Hz, *J* 9.5 Hz, *J* 6.0 Hz), 2.98 (ddd, 1H, H-7', *J* 13.0 Hz, *J* 10.0 Hz, *J* 5.0 Hz), 3.19 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 9.5 Hz, *J* 5.0 Hz), 3.84 (s, 3H, H-14), 3.87-3.83 (m, 1H, H-5), 3.92 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 10.0 Hz, *J* 6.0 Hz), 5.04 (dd, 1H, H-4, *J* 8.5 Hz, *J* 1.5 Hz), 6.85 (d, 1H, H-10, *J* 7.5 Hz), 6.90 (br t, 1H, H-12, *J* 7.5 Hz), 7.18-7.23 (m, 2H, H-11 and H-13). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 12.5 (C-19), 15.8 (C-16 or C-17), 18.5 (C-17 or C-16), 19.3 (C-18), 28.2 (C-

15), 28.3 (C-7), 40.9 (C-6), 46.9 (C-3), 55.2 (C-14), 65.8 (C-5), 83.4 (C-4), 110.2 (C-10), 120.6 (C-12), 126.7 (C-8), 127.9 (C-11), 130.7 (C-13), 157.5 (C-9), 171.8 (C-2). ***m/z*** (ES-) 333 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2O_4^+$) requires ***m/z*** 335.1965, found ***m/z*** 335.1965.

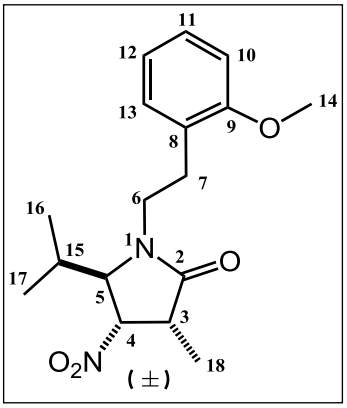
A.2.7.6. 5-Isopropyl-3-methyl-1-[2-(2-methoxyphenyl)ethyl]-4-nitropyrrolidin-2-one 193afc

Prepared according to the general procedure **C** with methyl 2-methyl-3-nitropropanoate **194c**, 2-(2-methoxyphenyl)ethanamine **167f** and isobutyraldehyde **166a**. **193afc** (106 mg, 80% yield) was obtained as a separable mixture of two diastereoisomers (dr 3:1) which were isolated by flash column chromatography (gradient petroleum ether / ethyl acetate from 5:1 to 1:1, R_{fmajor} = 0.15 and R_{fminor} = 0.10 in petroleum ether /ethyl acetate 5:1).



Major diastereoisomer (60% yield, isolated as a light yellow oil).

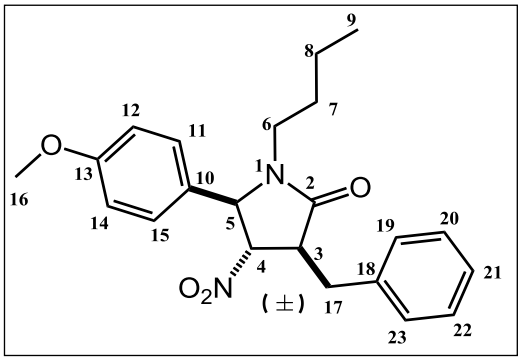
IR (cm^{-1}) ν_{max} 1698 (C=O), 1601 (C=C aromatic), 1588 (C=C aromatic), 1555 (NO_2), 1495 (C=C aromatic), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.77 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 0.93 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 1.35 (d, 3H, H-18, *J* 7.5 Hz), 2.19-2.31 (m, 1H, H-15), 2.76-2.84 (m, 1H, H-7), 2.92-3.07 (m, 3H, H-3, H-6 and H-7'), 3.85 (s, 3H, H-14), 3.96 (dd, 1H, H-5, *J* 5.5 Hz, *J* 3.5 Hz), 4.01-4.09 (m, 1H, H-6'), 4.41-4.46 (m, 1H, H-4), 6.86 (br d, 1H, H-10, *J* 7.5 Hz), 6.90 (br t, 1H, H-12, *J* 7.5 Hz), 7.17 (dd, 1H, H-13, *J* 7.5 Hz, *J* 1.5 Hz), 7.23 (td, 1H, H-11, *J* 7.5 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.7 (C-17 or C-18), 14.8 (C-18 or C-17), 17.6 (C-16), 26.8 (C-15), 28.0 (C-7), 40.1 (C-6), 42.9 (C-3), 55.2 (C-14), 64.1 (C-5), 85.9 (C-4), 110.3 (C-10), 120.7 (C-12), 126.4 (C-8), 128.1 (C-11), 130.6 (C-13), 157.5 (C-9), 171.8 (C-2). ***m/z*** (ES-) 319 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}N_2O_4Na^+$) requires ***m/z*** 343.1628, found ***m/z*** 343.1627.



Minor diastereoisomer (20% yield, isolated as a light yellow oil).

IR (cm^{-1}) ν_{max} 1697 (C=O), 1602 (C=C aromatic), 1588 (C=C aromatic), 1556 (NO_2), 1495 (C=C aromatic), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.78 (d, 3H, H-16 or H-17, *J* 7.0 Hz), 1.00 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 1.16 (d, 3H, H-18, *J* 7.5 Hz), 2.12-2.23 (m, 1H, H-15), 2.80-2.93 (m, 2H, H-7 and H-3), 2.95-3.04 (m, 1H, H-7'), 3.13-3.22 (m, 1H, H-6), 3.85 (s, 3H, H-14), 3.90-4.03 (m, 2H, H-5 and H-6'), 4.96 (dd, 1H, H-4, *J* 9.0 Hz, *J* 1.5 Hz), 6.85 (d, 1H, H-10, *J* 8.0 Hz), 6.89 (br t, 1H, H-12, *J* 7.5 Hz), 7.18-7.23 (m, 2H, H-11 and H-13). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 10.3 (C-18), 15.5 (C-16 or C-17), 18.4 (C-17 or C-16), 27.9 (C-15), 28.3 (C-7), 39.8 (C-3), 40.8 (C-6), 55.2 (C-14), 65.1 (C-5), 83.9 (C-4), 110.2 (C-10), 120.6 (C-12), 126.6 (C-8), 128.0 (C-11), 130.6 (C-13), 157.5 (C-9), 172.2 (C-2). ***m/z*** (ES-) 319 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}N_2O_4Na^+$) requires ***m/z*** 343.1628, found ***m/z*** 343.1629.

A.2.7.7. 1-Butyl-3-benzyl-5-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 193baa

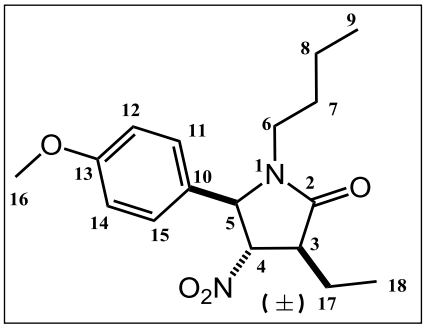


Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, butylamine **167a** and *p*-methoxybenzaldehyde **166b**. **193baa** (158 mg, 80% yield) was obtained as a mixture of two diastereoisomers (dr 11:1). The major diastereoisomers was isolated by flash column chromatography (gradient petroleum ether / ethyl acetate from 10:1 to 5:1, R_{fmajor} = 0.51).

IR (cm^{-1}) ν_{max} 1699 (C=O), 1612 (C=C aromatic), 1586 (C=C aromatic), 1556 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.84 (t, 3H, H-9, *J* 7.5 Hz), 1.13-1.29 (m, 2H, H-8), 1.30-1.39 (m, 2H, H-7), 2.48 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.12 (dd, 1H, H-17, *J* 14.0 Hz, *J* 5.5 Hz), 3.38 (dd, 1H, H-17', *J* 14.0 Hz, *J* 5.5 Hz), 3.51 (dt, 1H, H-3, *J* 7.5 Hz, *J* 5.5 Hz), 3.63 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.77 (s, 3H, H-16), 4.66 (dd, 1H, H-4, *J* 7.5 Hz, *J* 5.5 Hz), 4.89 (d, 1H, H-5, *J* 5.5 Hz), 6.60 (d, 2H, H-11 and H-15, *J* 8.5 Hz), 6.75 (d, 2H, H-12 and H-14, *J* 8.5 Hz), 7.19-7.24 (m, 2H, H-19 and H-23), 7.27-7.35 (m, 3H, H-20, H-21 and H-22). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.5 (C-7), 34.1 (C-17), 40.5 (C-6), 48.6 (C-

3), 55.4 (C-16), 63.2 (C-5), 88.6 (C-4), 114.6 (C-12 and C-14), 127.2 (C-21), 128.2 (C-11 and C-15), 128.5 (C-10), 129.0 (C-20 and C-22), 129.9 (C-19 and C-23), 136.3 (C-18), 160.1 (C-13), 170.3 (C-2). ***m/z*** (ES-) 381 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{22}H_{26}N_2O_4Na^+$) requires ***m/z*** 405.1785, found ***m/z*** 405.1786.

A.2.7.8. 1-Butyl-3-ethyl-5-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 193bab



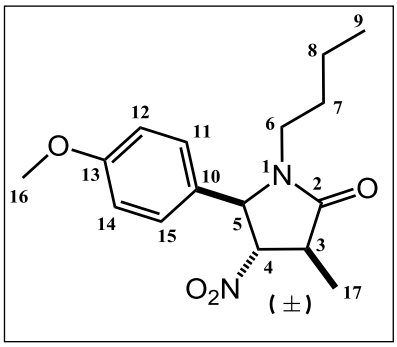
Prepared according to the general procedure **C** with methyl 2-ethyl-3-nitropropanoate **194b**, butylamine **167a** and *p*-methoxybenzaldehyde **166b**. **193bab** (158 mg, 80% yield) was obtained as a mixture of two diastereomers (dr 10:1). The major diastereomer was isolated by flash column chromatography (petroleum ether / ethyl acetate 7:1, R_{fmajor} = 0.53 in petroleum ether / ethyl acetate 5:1).

IR (cm^{-1}) ν_{max} 1701 (C=O), 1613 (C=C aromatic), 1587 (C=C aromatic), 1556 (NO_2), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.85 (t, 3H, H-9, *J* 7.5 Hz), 1.01 (t, 3H, H-18, *J* 7.5 Hz), 1.16-1.30 (m, 2H, H-8), 1.36-1.43 (m, 2H, H-7), 1.71 (dquint, 1H, H-17, *J* 14.5 Hz, *J* 7.5 Hz), 2.03 (dqd, 1H, H-17', *J* 14.5 Hz, *J* 7.5 Hz, *J* 4.5 Hz), 2.56 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.12 (dt, 1H, H-3, *J* 7.5 Hz, *J* 4.5 Hz), 3.73 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.82 (s, 3H, H-16), 4.67 (dd, 1H, H-4, *J* 7.5 Hz, *J* 5.5 Hz), 4.95 (d, 1H, H-5, *J* 5.5 Hz), 6.94 (d, 2H, H-12 and H-14, *J* 8.5 Hz), 7.12 (d, 2H, H-11 and H-15, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 10.7 (C-18), 13.6 (C-9), 19.8 (C-8), 22.9 (C-17), 28.6 (C-7), 40.4 (C-6), 48.7 (C-3), 55.3 (C-16), 63.8 (C-5), 91.0 (C-4), 114.8 (C-12 and C-14), 128.1 (C-11 and C-15), 128.4 (C-10), 160.3 (C-13), 171.4 (C-2). ***m/z*** (ES-) 319 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{24}N_2O_4Na^+$) requires ***m/z*** 321.1809, found ***m/z*** 321.1809.

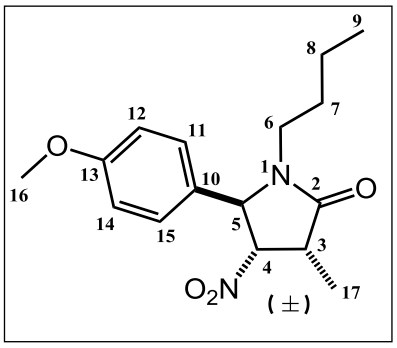
A.2.7.9. 1-Butyl-5-(4-methoxyphenyl)-3-methyl-4-nitropyrrolidin-2-one 193bac

Prepared according to the general procedure **C** with methyl 2-methyl-3-nitropropanoate **193c**, butylamine **167a** and *p*-methoxybenzaldehyde **166b**. **193bac** (160 mg, 78% yield) was obtained as a separable mixture of two diastereoisomers (dr 3:1) which were isolated by flash column

chromatography (gradient petroleum ether / diethyl ether from 3:1 to 2:1, R_{fmajor} = 0.20 and R_{fminor} = 0.08 in petroleum ether / diethyl ether 2:1).

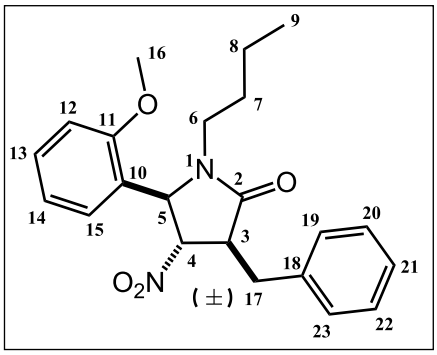


Major diastereoisomer (63% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1702 (C=O), 1613 (C=C aromatic), 1587 (C=C aromatic), 1556 (NO_2), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.84 (t, 3H, H-9, *J* 7.5 Hz), 1.22 (quintd, 2H, H-8, *J* 14.0 Hz, *J* 7.5 Hz), 1.35-1.41 (m, 2H, H-7), 1.43 (d, 3H, H-17, *J* 7.5 Hz), 2.55 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.16 (quint, 1H, H-3, *J* 7.5 Hz), 3.72 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.81 (s, 3H, H-16), 4.57 (dd, 1H, H-4, *J* 7.5 Hz, *J* 6.0 Hz), 4.97 (d, 1H, H-5, *J* 6.0 Hz), 6.93 (d, 2H, H-12 and H-14, *J* 8.5 Hz), 7.14 (d, 2H, H-11 and H-15, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 15.1 (C-17), 19.8 (C-8), 28.6 (C-7), 40.4 (C-6), 42.5 (C-3), 55.3 (C-16), 63.4 (C-5), 93.2 (C-4), 114.8 (C-12 and C-14), 128.0 (C-10), 128.3 (C-11 and C-15), 160.4 (C-13), 171.8 (C-2). ***m/z*** (ES-) 305 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}N_2O_4Na^+$) requires ***m/z*** 329.1472, found ***m/z*** 329.1469.



Minor diastereoisomer (15% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1699 (C=O), 1612 (C=C aromatic), 1586 (C=C aromatic), 1555 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.90 (t, 3H, H-9, *J* 7.5 Hz), 1.22 (d, 3H, H-17, *J* 8.0 Hz), 1.28-1.42 (m, 2H, H-8), 1.47-1.55 (m, 2H, H-7), 2.62-2.80 (m, 1H, H-6), 3.13 (quint, 1H, H-3, *J* 8.0 Hz), 3.77-3.81 (m, 1H, H-6'), 3.82 (s, 3H, H-16), 4.97 (dd, 1H, H-4, *J* 8.0 Hz, *J* 1.5 Hz), 5.06 (d, 1H, H-5, *J* 1.5 Hz), 6.93 (d, 2H, H-12 and H-14, *J* 9.0 Hz), 7.11 (d, 2H, H-11 and H-15, *J* 9.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 10.0 (C-17), 13.7 (C-9), 19.9 (C-8), 28.8 (C-7), 38.6 (C-3), 40.9 (C-6), 55.4 (C-16), 63.0 (C-5), 89.9 (C-4), 114.9 (C-12 and C-14), 127.6 (C-11 and C-15), 127.7 (C-10), 160.3 (C-13), 172.2 (C-2). ***m/z*** (ES-) 305 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}N_2O_4Na^+$) requires ***m/z*** 329.1472, found ***m/z*** 329.1468.

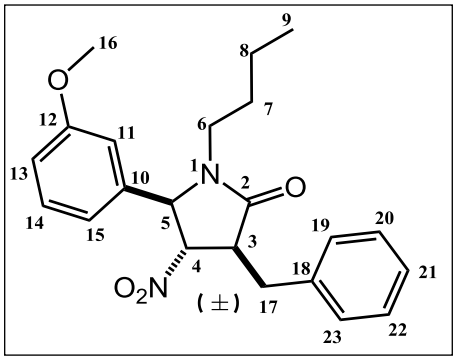
A.2.7.10. 3-Benzyl-1-butyl-5-(2-methoxyphenyl)-4-nitropyrrolidin-2-one 193faa



Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, butylamine **167a** and *o*-methoxybenzaldehyde **166f**. **193faa** (125 mg, 73% yield) was obtained as a mixture of two diastereomers (dr >10:1). The major diastereoisomer was isolated by flash column chromatography (petroleum ether / diethyl ether from 4:1, R_{fmajor} = 0.47 and R_{fminor} = 0.13).

IR (cm^{-1}) ν_{max} 1700 (C=O), 1602 (C=C aromatic), 1556 (NO_2), 1369 (NO_2). **^{1}H NMR** (DMSO, 500 MHz, T= 373 K) δ_H 0.82 (t, 3H, H-9, *J* 7.5 Hz), 1.13-1.27 (m, 2H, H-8), 1.28-1.41 (m, 2H, H-7), 2.56 (m, 1H, H-6), 2.93 (dd, 1H, H-17, *J* 14.0 Hz, *J* 8.0 Hz), 3.20 (dd, 1H, H-17', *J* 14.0 Hz, *J* 5.0 Hz), 3.48-3.58 (m, 2H, H-3 and H-6'), 3.74 (s, 3H, H-16), 4.92 (t, 1H, H-4, *J* 5.5 Hz), 5.23 (d, 1H, H-5, *J* 5.5 Hz), 6.92-6.97 (m, 2H, H_{Ar}), 7.07-7.12 (m, 1H, H_{Ar}), 7.15-7.21 (m, 2H, H_{Ar}), 7.21-7.31 (m, 3H, H_{Ar}), 7.35-7.43 (m, 1H, H_{Ar}). **^{13}C NMR** (DMSO, 125 MHz, T= 373 K) δ_C 14.0 (C-9), 20.1 (C-8), 29.2 (C-7), 35.4 (C-17), 41.2 (C-6), 49.1 (C-3), 56.6 (C-16), 60.8 (C-5), 89.2 (C-4), 113.0 (C_{Ar}-H), 121.7 (C_{Ar}-H), 125.1 (C_{quat}), 127.5 (C_{Ar}-H), 129.3 (2xC_{Ar}-H), 129.4 (C_{Ar}-H), 130.0 (2xC_{Ar}-H), 131.3 (C_{Ar}-H), 138.3 (C_{quat}), 158.3 (C_{quat}), 171.3 (C-2). ***m/z*** (ES-) 381 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_4Na^+$) requires ***m/z*** 405.1785, found ***m/z*** 405.1784.

A.2.7.11. 3-Benzyl-1-butyl-5-(3-methoxyphenyl)-4-nitropyrrolidin-2-one 193gaa



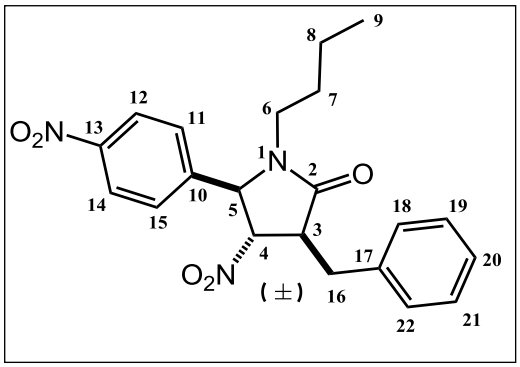
Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, butylamine **167a** and *m*-methoxybenzaldehyde **166g**. **193gaa** (140 mg, 82% yield) was obtained as a mixture of two diastereoisomers (dr 12:1). The major diastereoisomer was isolated by flash column chromatography (petroleum ether / diethyl ether from 4:1, R_{fmajor} = 0.12 and R_{fminor} = 0.05).

IR (cm^{-1}) ν_{max} 1701 (C=O), 1602 (C=C aromatic), 1556 (NO_2), 1369 (NO_2). **^{1}H NMR** (DMSO, 500 MHz, T= 373 K) δ_H 0.81 (t, 3H, H-9, *J* 7.5 Hz), 1.13-1.27 (m, 2H, H-8), 1.29-1.42 (m, 2H, H-7), 2.61 (ddd, 1H, H-6,

J 14.0 Hz, *J* 7.5 Hz, *J* 6.0 Hz), 3.10-3.23 (m, 2H, H-17), 3.44-3.54 (m, 1H, H-6'), 3.57-3.65 (m, 1H, H-3), 3.75 (s, 3H, H-16), 4.83 (dd, 1H, H-4, *J* 7.0 Hz, *J* 6.0 Hz), 5.01 (d, 1H, H-5, *J* 6.0 Hz), 6.61 (d, 1H, H_{Ar}, *J* 7.5 Hz), 6.67 (br s, 1H, H_{Ar}), 6.95 (dd, 2H, H_{Ar}, *J* 8.0 Hz, *J* 2.0 Hz), 7.20-7.36 (m, 5H, H_{Ar}). **^{13}C NMR** (DMSO, 125 MHz, T= 373 K) δ_C 14.0 (C-9), 20.2 (C-8), 29.1 (C-7), 35.0 (C-17), 41.3 (C-6), 48.6 (C-3), 56.2 (C-16), 64.4 (C-5), 90.0 (C-4), 114.0 (C_{Ar}-H), 115.7 (C_{Ar}-H), 120.4 (C_{Ar}-H), 127.6 (C_{Ar}-H), 129.3 (2x C_{Ar}-H), 130.2 (2x C_{Ar}-H), 131.0 (C_{Ar}-H), 138.1 (C_{quat}), 139.6 (C_{quat}), 160.9 (C-12), 171.2 (C-2). ***m/z*** (ES-) 381 ([M-H]$^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_4Na^+$) requires ***m/z*** 405.1785, found ***m/z*** 405.1782.

A.2.7.12. 3-Benzyl-1-butyl-5-(4-nitro)-4-nitropyrrolidin-2-one 193oaa

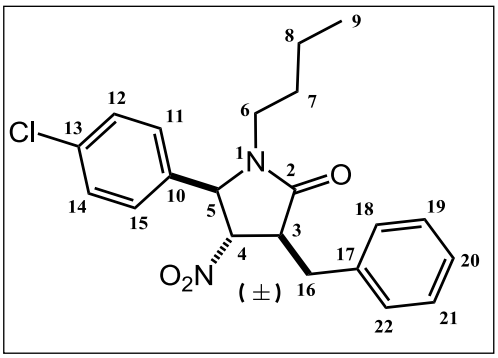
Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, butylamine **167a** and *p*-nitrobenzaldehyde **166o**. **193oaa** (170 mg, 80% yield) was obtained as an unseparable mixture of two diastereoisomers (dr 11:1). The major diastereoisomer was purified by flash column chromatography (petroleum ether / diethyl ether 7:1, R_{fmajor} = 0.30).



IR (cm^{-1}) ν_{max} 1700 (C=O), 1603 (C=C aromatic), 1556 (NO_2), 1524 (NO_2), 1496 (C=C aromatic), 1418 (NO_2), 1349 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (t, 3H, H-9, *J* 7.5 Hz), 1.12-1.28 (m, 2H, H-8), 1.29-1.41 (m, 2H, H-7), 2.41 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.02-3.13 (m, 1H, H-16), 3.49-3.62 (m, 2H, H-16' and H-3), 3.70 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.63 (dd, 1H, H-4, *J* 7.0 Hz, *J* 5.5 Hz), 5.07 (d, 1H, H-5, *J* 5.5 Hz), 6.75 (d, 2H, H-11 and H-15, *J* 8.5 Hz), 7.19-7.24 (m, 2H, H-18 and H-22), 7.29-7.40 (m, 3H, H-19, H-20, and H-21), 8.06 (d, 2H, H-12 and H-14, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.5 (C-7), 33.9 (C-16), 40.8 (C-6), 48.3 (C-3), 62.5 (C-5), 87.1 (C-4), 124.5 (C-12 and C-14), 127.6 (C-20), 127.9 (C-11 and C-15), 129.2 (C-19 and C-21), 130.1 (C-18 and C-22), 136.0 (C-17), 144.2 (C-10), 148.4 (C-13), 170.4 (C-2). ***m/z*** (ES+) 420 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{23}N_3O_5Na^+$) requires ***m/z*** 420.1530, found ***m/z*** 420.1534.

A.2.7.13. 3-Benzyl-1-butyl-5-(4-chlorophenyl)-4-nitropyrrolidin-2-one 193eaa

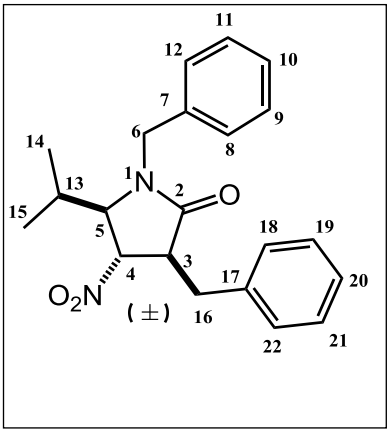
Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, butylamine **167a** and *p*-chlorobenzaldehyde **166e**. **193eaa** (170 mg, 80% yield) was obtained as an unseparable mixture of two diastereoisomers (dr 10:1). The major diastereoisomer was purified by flash column chromatography (petroleum ether / diethyl ether 7:1, R_{fmajor} = 0.32).



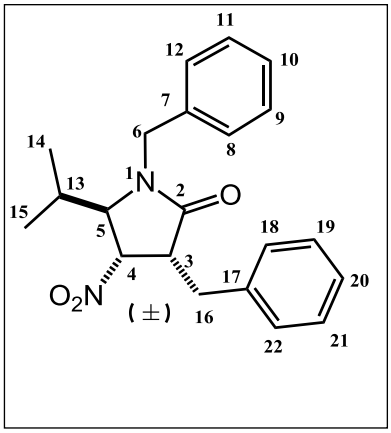
IR (cm^{-1}) ν_{max} 1702 (C=O), 1602 (C=C aromatic), 1582 (C=C aromatic), 1556 (NO_2), 1494 (C=C aromatic), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.85 (t, 3H, H-9, *J* 7.5 Hz), 1.16-1.29 (m, 2H, H-8), 1.30-1.39 (m, 2H, H-7), 2.45 (dt, 1H, H-6, *J* 14.0 Hz, *J* 7.0 Hz), 3.10 (dd, 1H, H-16, *J* 14.0 Hz, *J* 5.0 Hz), 3.45 (dd, 1H, H-16', *J* 14.0 Hz, *J* 5.0 Hz), 3.54 (dt, 1H, H-3, *J* 7.5 Hz, *J* 5.0 Hz), 3.66 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.63 (dd, 1H, H-4, *J* 7.5 Hz, *J* 6.0 Hz), 4.93 (d, 1H, H-5, *J* 6.0 Hz), 6.56 (d, 2H, H-11 and H-15, *J* 8.0 Hz), 7.19-7.24 (m, 4H, H-12, H-14, H-18 and H-22), 7.31-7.34 (m, 3H, H-19, H-20 and H-21). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.5 (C-7), 34.0 (C-16), 40.6 (C-6), 48.5 (C-3), 62.9 (C-5), 87.9 (C-4), 127.3 (C-20), 128.2 (C-11 and C-15), 129.1 (C-19 and C-21), 129.5 (C-12 and C-14), 130.0 (C-18 and C-22), 135.2 (C-13 or C-10), 135.4 (C-10 or C-13), 136.2 (C-17), 170.4 (C-2). ***m/z*** (ES+) 387 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{23}N_2O_3ClNa^+$) requires ***m/z*** 409.1289, found ***m/z*** 409.1281.

A.2.7.14. 1,3-Dibenzyl-5-isopropyl-4-nitropyrrolidin-2-one 193aba

Prepared according to the general procedure **C** with methyl 2-benzyl-3-nitropropanoate **194a**, benzylamine **167b** and isobutyraldehyde **166a**. **193aba** (90 mg, 64% yield) was obtained as a separable mixture of two diastereoisomers (dr 3:1) which were isolated by flash column chromatography (petroleum ether / diethyl ether 3:1 then 2:1, R_{fmajor} = 0.30 and R_{fminor} = 0.11 in petroleum ether / diethyl ether 2:1).



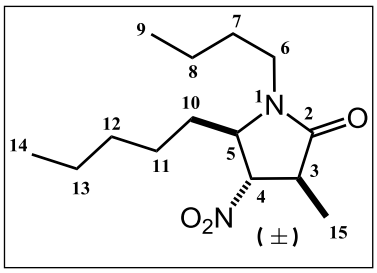
Major diastereoisomer (45% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1700 (C=O), 1604 (C=C aromatic), 1584 (C=C aromatic), 1557 (NO_2), 1496 (C=C aromatic), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.29 (d, 3H, H-14 or H-15, *J* 6.5 Hz), 0.76 (d, 3H, H-15 or H-14, *J* 6.5 Hz), 2.07 (septd, 1H, H-13, *J* 6.5 Hz, *J* 4.0 Hz), 3.18 (dd, 1H, H-16, *J* 14.5 Hz, *J* 5.5 Hz), 3.23 (dd, 1H, H-16', *J* 14.5 Hz, *J* 6.5 Hz), 3.48 (m, 1H, H-3), 3.78-3.82 (m, 2H, H-5 and H-6), 4.64 (dd, 1H, H-4, *J* 6.5 Hz, *J* 5.5 Hz), 5.16 (d, 1H, H-6', *J* 15.0 Hz), 7.21-7.39 (m, 10H, $H_{Ar\text{-}benzyl}$). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-14 or C-15), 17.4 (C-15 or C-14), 26.9 (C-13), 33.9 (C-16), 44.5 (C-6), 49.5 (C-3), 63.5 (C-5), 81.5 (C-4), 127.3 (C_{Ar}-H), 127.9 (C-8 and C-12), 128.0 (2x C_{Ar}-H), 128.9 (2x C_{Ar}-H), 129.0 (C_{Ar}-H), 129.7 (C-18 and C-22), 134.8 (C-7), 136.3 (C-17), 170.9 (C-2). ***m/z*** (ES+) 353 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2O_3Na^+$) requires ***m/z*** 375.1679, found ***m/z*** 375.1680.



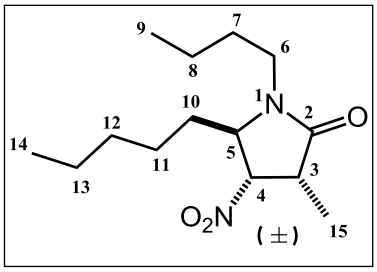
Minor diastereoisomer (19% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1701 (C=O), 1604 (C=C aromatic), 1584 (C=C aromatic), 1556 (NO_2), 1496 (C=C aromatic), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.76 (d, 3H, H-14 or H-15, *J* 7.0 Hz), 0.93 (d, 3H, H-15 or H-14, *J* 7.0 Hz), 2.10 (septd, 1H, H-13, *J* 7.0 Hz, *J* 4.0 Hz), 2.63 (dd, 1H, H-16, *J* 15.0 Hz, *J* 11.0 Hz), 3.14 (ddd, 1H, H-3, *J* 11.0 Hz, *J* 7.5 Hz, *J* 4.0 Hz), 3.53 (d, 1H, H-5, *J* 4.0 Hz), 3.55 (dd, 1H, H-16', *J* 15.0 Hz, *J* 4.0 Hz), 4.02 (d, 1H, H-6, *J* 15.0 Hz), 4.85 (d, 1H, H-4, *J* 7.5 Hz), 5.18 (d, 1H, H-6', *J* 15.0 Hz), 7.18 (br d, 2H, $H_{Ar\text{-}benzyl}$, *J* 7.5 Hz), 7.23-7.40 (m, 8H, $H_{Ar\text{-}benzyl}$).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 15.7 (C-14 or C-15), 18.3 (C-15 or C-14), 27.9 (C-13), 31.6 (C-16), 45.1 (C-6), 47.4 (C-3), 65.7 (C-5), 82.5 (C-4), 126.9 (C_{Ar}-H), 128.0 (C_{Ar}-H), 128.3 (2x C_{Ar}-H), 128.6 (3x C_{Ar}-H), 128.8 (4x C_{Ar}-H), 134.8 (C-7), 137.9 (C-17), 171.5 (C-2). ***m/z*** (ES-) 351 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2O_3Na^+$) requires ***m/z*** 375.1679, found ***m/z*** 375.1678.

A.2.7.15. 1-Butyl-3-methyl-4-nitro-5-pentylpyrrolidin-2-one 193nac

Prepared according to the general procedure **C** with methyl 2-methyl-3-nitropropanoate **194c** (150 mg), butylamine **167a** and hexanal **166n**. **193nac** (150mg, 55% yield) was obtained as a separable mixture of two diastereoisomers (dr 3.5:1) which were separated by flash column chromatography (petroleum ether / ethyl acetate 7:1, R_{fmajor} = 0.32 and R_{fminor} = 0.20).

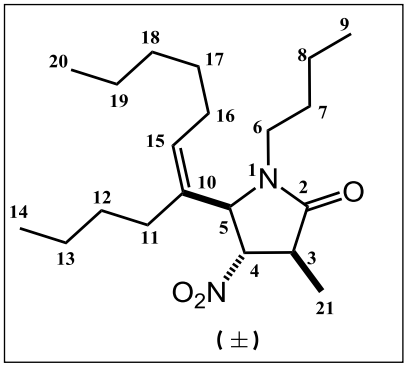


Major diastereoisomer (43% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1695 (C=O), 1554 (NO_2), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89-0.92 (m, 3H, H-14), 0.94 (t, 3H, H-9, *J* 7.5 Hz), 1.26-1.37 (m, 8H, H-8, H-11, H-12 and H-13), 1.39 (d, 3H, H-15, *J* 7.0 Hz), 1.44-1.57 (m, 3H, H-7 and H-10), 1.81-2.04 (m, 1H, H-10'), 2.86 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.08 (quint, 1H, H-3, *J* 7.0 Hz), 3.74 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 8.5 Hz, *J* 7.5 Hz), 4.03 (ddd, 1H, H-5, *J* 8.5 Hz, *J* 5.5 Hz, *J* 3.5 Hz), 4.48 (dd, 1H, H-4, *J* 7.0 Hz, *J* 5.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 13.9 (C-14), 15.3 (C-15), 19.9 (C-8), 22.4 (C-13), 23.4 (C-11), 29.0 (C-7), 31.5 (C-12), 31.7 (C-10), 40.0 (C-6), 42.7 (C-3), 59.5 (C-5), 89.6 (C-4), 171.7 (C-2). ***m/z*** (ES+) 293 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{26}N_2O_3Na^+$) requires ***m/z*** 293.1836, found ***m/z*** 293.1838.



Minor diastereoisomer (12% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1695 (C=O), 1555 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.88-0.93 (m, 3H, H-14), 0.96 (t, 3H, H-9, *J* 7.5 Hz), 1.19 (d, 3H, H-15, *J* 7.5 Hz), 1.24-1.49 (m, 9H, H-8, H-10, H-11, H-12 and H-13), 1.52-1.59 (m, 2H, H-7), 1.71-1.78 (m, 1H, H-10'), 2.90 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 5.5 Hz), 2.98 (quint, 1H, H-3, *J* 7.5 Hz), 3.74 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.98 (ddd, 1H, H-5, *J* 9.0 Hz, *J* 3.5 Hz, *J* 1.5 Hz), 4.97 (dd, 1H, H-4, *J* 7.5 Hz, *J* 1.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 9.9 (C-15), 13.7 (C-9), 13.9 (C-14), 20.0 (C-8), 22.4 (C-13), 24.5 (C-11), 29.0 (C-7), 30.8 (C-10), 31.5 (C-12), 39.1 (C-3), 40.5 (C-6), 59.9 (C-5), 87.2 (C-4), 171.6 (C-2). ***m/z*** (ES+) 293 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{26}N_2O_3Na^+$) requires ***m/z*** 293.1836, found ***m/z*** 293.1834.

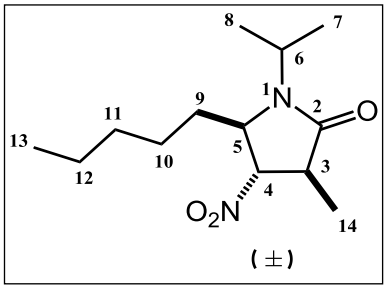
Side product isolated: 1-butyl-4-nitro-5-[(5*Z*)-undec-5-en-5-yl]pyrrolidin-2-one 196



IR ν_{max} (cm^{-1}) 1704 (C=O), 1556 (NO_2), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.87-1.02 (m, 9H), 1.09-1.60 (m, 17H), 1.76-1.87 (m, 1H), 2.04-2.19 (m, 3H), 2.64 (dt, 1H, H-6, *J* 13.5 Hz, *J* 7.0 Hz), 3.05-3.19 (m, 1H, H-3), 3.67-3.80 (m, 1H, H-6'), 4.37 (d, 1H, H-5, *J* 4.5 Hz), 4.51 (dd, 1H, H-4, *J* 6.0 Hz, *J* 4.5 Hz), 5.40 (t, 1H, H-15, *J* 7.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (CH_3), 13.8 (CH_3), 14.8 (CH_3), 15.5 (CH_3), 15.5 (CH_2), 19.9 (CH_2), 22.6 (CH_2), 23.0 (CH_2), 27.8 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 31.4 (CH_2), 31.5 (CH_2),40.6 (C-6), 42.5 (C-3), 66.4 (C-5), 90.0 (C-4), 133.3 (C-15), 134.1 (C-10), 172.5 (C-2). ***m/z*** (ES-) 351 ($[M-H]^-$, 100%), HRMS (ES-) exact mass calculated for $[M-H]^-$ ($C_{20}H_{35}N_2O_3^-$) requires ***m/z*** 351.2653, found ***m/z*** 351.2643.

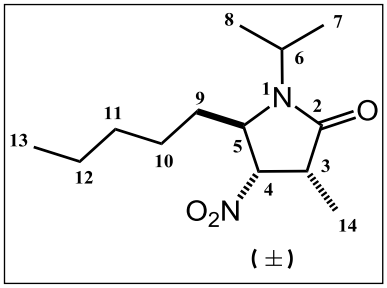
A.2.7.16. 1-Isopropyl-3-methyl-4-nitro-5-pentylpyrrolidin-2-one 193nmc

Prepared according to the general procedure **A** with methyl 2-methyl-3-nitropropanoate **194c**, isopropylamine **167m** and hexanal **166n**. **193nmc** (191mg, 55% yield) was obtained as a separable mixture of two diastereoisomers (dr 5:1) which were separated by flash column chromatography (petroleum ether / diethyl ether 2:1), R_{fmajor} = 0.51 and R_{fminor} = 0.35 (in petroleum ether /diethyl ether 1:1).



Major diastereoisomer (47% yield, isolated as a light yellow oil).

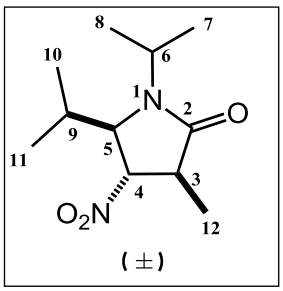
IR (cm^{-1}) ν_{max} 1690 (C=O), 1553 (NO_2), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.96 (t, 3H, H-13, *J* 6.5 Hz), 1.31-1.50 (m, 15H, H-7, H-8, H-10, H-11, H-12 and H-14), 1.52-1.59 (m, 1H, H-9), 1.93-2.03 (m, 1H, H-9'), 3.06 (qd, 1H, H-3, *J* 7.5 Hz, *J* 4.5 Hz),4.02-4.13 (m, 2H, H-5 and H-6), 4.54 (t, 1H, H-4, J 4.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.3 (C-13), 16.5 (C-14), 19.8 (C-7 or C-8), 21.5 (C-8 or C-7), 22.9 (C-12), 24.5 (C-10), 31.9 (C-11), 35.1 (C-9), 43.6 (C-3), 45.9 (C-6), 61.1 (C-5), 89.9 (C-4), 172.7 (C-2). ***m/z*** (ES+) 279 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{24}N_2O_3Na^+$) requires ***m/z*** 279.1679, found ***m/z*** 279.1680.



Minor diastereoisomer (8% yield, isolated as a light yellow oil). **IR** (cm^{-1}) ν_{max} 1676 (C=O), 1554 (NO_2), 1366 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.96 (t, 3H, H-13, *J* 6.5 Hz), 1.31-1.50 (m, 15H, H-7, H-8, H-10, H-11, H-12 and H-14), 1.52-1.59 (m, 1H, H-9), 1.93-2.03 (m, 1H, H-9'), 3.06 (qd, 1H, H-3, *J* 7.5 Hz, *J* 4.5 Hz),4.02-4.13 (m, 2H, H-5 and H-6), 4.54 (t, 1H, H-4, *J* 4.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.3 (C-13), 16.5 (C-14), 19.8 (C-7 or C-8), 21.5 (C-8 or C-7), 22.9 (C-12), 24.5 (C-10), 31.9 (C-11), 35.1 (C-9), 43.6 (C-3), 45.9 (C-6), 61.1 (C-5), 89.9 (C-4), 172.7 (C-2). ***m/z*** (ES+) 279 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{24}N_2O_3Na^+$) requires ***m/z*** 279.1679, found ***m/z*** 279.1683.

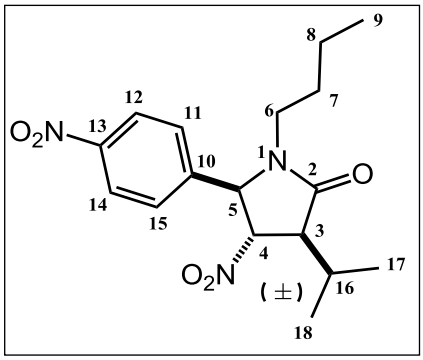
A.2.7.17. 1,5-Diisopropyl-3-methyl-4-nitropyrrolidin-2-one 193amc

Prepared according to the general procedure **C** with methyl 2-methyl-3-nitropropanoate **194c**, isopropylamine **167m** and isobutyraldehyde **166a**. **193amc** (108 mg, 70% yield) was obtained as an inseparable mixture of two diastereoisomers (dr 6:1) which was purified by flash column chromatography (gradient from petroleum ether / diethyl ether 4:1, R_f = 0.19) as a yellow oil.



IR (cm^{-1}) ν_{max} 1687 (C=O), 1555 (NO_2), 1361 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.85 (d, 3H, H-10 or H-11, *J* 7.0 Hz), 1.02 (d, 3H, H-11 or H-10, *J* 7.0 Hz), 1.30 (d, 3H, H-7 or H-8, *J* 7.0 Hz), 1.36 (d, 3H, H-8 or H-7, *J* 7.0 Hz), 1.39 (d, 3H, H-12, *J* 7.5 Hz), 2.21 (septd, 1H, H-9, *J* 7.0 Hz, *J* 4.0 Hz), 3.02 (qd, 1H, H-3, *J* 7.5 Hz, *J* 5.0 Hz), 3.99 (sept, 1H, H-6, *J* 7.0 Hz), 4.06 (t, 1H, H-5, *J* 4.0 Hz), 4.48 (dd, 1H, H-4, *J* 5.0 Hz, *J* 4.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-10 or C-11), 15.1 (C-12), 18.2 (C-11 or C-10), 19.1 (C-7 or C-8), 20.6 (C-8 or C-7), 29.3 (C-9), 43.4 (C-3), 45.8 (C-6), 65.6 (C-5), 85.5 (C-4), 172.5 (C-2). ***m/z*** (ES-) 227 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{20}N_2O_3Na^+$) requires ***m/z*** 251.1366, found ***m/z*** 251.1367.

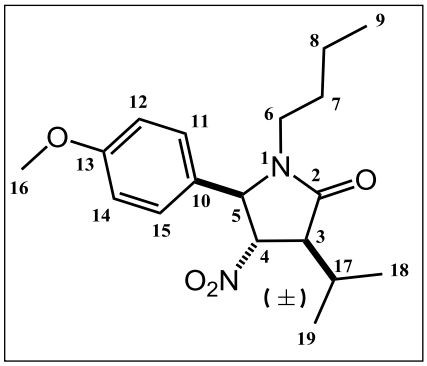
A.2.7.18. 1-Butyl-3-isopropyl-4-nitro-5-(4-nitrophenyl)pyrrolidin-2-one 193rad



Prepared according to the general procedure **C** with methyl 3-methyl-2-(nitromethyl)butanoate **194d**, butylamine **167a** and *p*-nitrobenzaldehyde **166r**. **193rad** (170mg, 85% yield) was obtained as a separable mixture of two diastereoisomers (dr 7:1). The major diastereoisomer was isolated by flash column chromatography (petroleum ether / diethyl ether 4:1, R_{fmajor} = 0.19) as a yellow solid.

mp 91-93 ˚C. **IR** (cm^{-1}) ν_{max} 1704 (C=O), 1606 (C=C aromatic), 1558 (NO_2), 1494 (C=C aromatic), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.87 (t, 3H, H-9, *J* 7.5 Hz), 0.97 (d, 3H, H-17 or H-18, *J* 7.0 Hz), 1.02 (d, 3H, H-18 or H-17, *J* 7.0 Hz), 1.17-1.33 (m, 2H, H-8), 1.37-1.48 (m, 2H, H-7), 2.44 (septd, 1H, H-16, *J* 7.0 Hz, *J* 4.5 Hz), 2.55 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.0 Hz, *J* 6.0 Hz), 3.29 (dd, 1H, H-3, *J* 7.5 Hz, *J* 4.5 Hz), 3.83 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.69 (dd, 1H, H-4, *J* 7.5 Hz, *J* 5.5 Hz), 5.06 (d, 1H, H-5, *J* 5.5 Hz), 7.43 (d, 2H, H-11 and H-15, *J* 8.5 Hz), 8.32 (d, 2H, H-12 and H-14, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 18.3 (C-17 or C-18), 19.5 (C-18 or C-17), 19.8 (C-8), 27.6 (C-16), 28.4 (C-7), 40.9 (C-6), 52.6 (C-3), 63.5 (C-5), 87.8 (C-4), 124.8 (C-12 and C-14), 127.8 (C-11 and C-15), 144.2 (C-10), 148.6 (C-13), 171.1 (C-2). ***m/z*** (ES+) 372 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{23}N_3O_5Na^+$) requires ***m/z*** 372.1530, found ***m/z*** 372.1516.

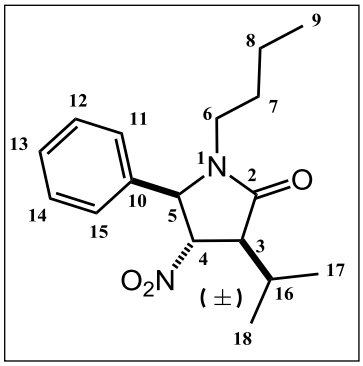
A.2.7.19. 1-Butyl-3-isopropyl-5-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 193bad



Prepared according to the general procedure **C** with methyl 3-methyl-2-(nitromethyl)butanoate **194d**, butylamine **167a** and *p*-methoxybenzaldehyde **166b**. **193bad** (156 mg, 82% yield) was obtained as a separable mixture of two diastereoisomers (dr 12:1). The major diastereoisomer was isolated by flash column chromatography (petroleum ether / diethyl ether 4:1, R_{fmajor} = 0.28) as a yellow oil.

IR (cm^{-1}) ν_{max} 1700 (C=O), 1613 (C=C aromatic), 1556 (NO_2), 1464 (C=C aromatic), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (t, 3H, H-9, *J* 7.5 Hz), 0.99 (d, 3H, H-18 or H-19, *J* 7.0 Hz), 1.02 (d, 3H, H-19 or H-18, *J* 7.0 Hz), 1.14-1.32 (m, 2H, H-8), 1.33-1.45 (m, 2H, H-7), 2.45 (septd, 1H, H-17, *J* 7.0 Hz, *J* 4.5 Hz), 2.54-2.64 (m, 1H, H-6), 3.25 (dd, 1H, H-3, *J* 8.0 Hz, *J* 4.5 Hz), 3.73 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.84 (s, 1H, H-16), 4.76 (dd, 1H, H-4, *J* 8.0 Hz, *J* 6.0 Hz), 4.85 (d, 1H, H-5, *J* 6.0 Hz), 6.85 (d, 2H, H-12 and H-14, *J* 9.0 Hz), 7.12 (d, 2H, H-11 and H-15, *J* 9.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 18.2 (C-18 or C-19), 19.5 (C-19 or C-18), 19.9 (C-8), 27.5 (C-17), 28.5 (C-7), 40.5 (C-6), 52.9 (C-3), 55.4 (C-16), 64.1 (C-5), 88.9 (C-4), 114.8 (C-12 and C-14), 128.1 (C-11 and C-15), 128.6 (C-10), 160.4 (C-13), 170.9 (C-2). ***m/z*** (ES+) 335 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2O_4Na^+$) requires ***m/z*** 357.1785, found ***m/z*** 357.1782.

A.2.7.20. 1-Butyl-3-isopropyl-4-nitro-5-phenylpyrrolidin-2-one 193sad

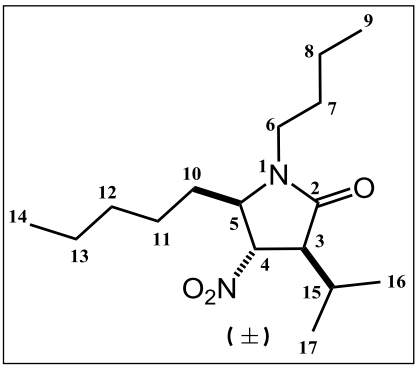


Prepared according to the general procedure **C** with methyl 3-methyl-2-(nitromethyl)butanoate **194d**, butylamine **167a** and benzaldehyde **166s**. **193sad** (139 mg, 80% yield) was obtained as a separable mixture of two diastereoisomers (dr 13:1). The major diastereoisomer was isolated by flash column chromatography (petroleum ether / diethyl ether 4:1, R_{fmajor} = 0.56) as a yellow oil

IR (cm^{-1}) ν_{max} 1702 (C=O), 1604 (C=C aromatic), 1557 (NO_2), 1493 (C=C aromatic), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.86 (t, 3H, H-9, *J* 7.5 Hz), 0.98 (d, 3H, H-17 or H-18, *J* 7.0 Hz), 1.02 (d, 3H, H-18 or H-17, *J* 7.0 Hz), 1.17-1.32 (m, 2H, H-8), 1.37-1.45 (m, 2H, H-7), 2.45 (septd, 1H, H-16, *J* 7.0 Hz, *J* 4.5 Hz), 2.59 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 7.5 Hz, *J* 6.0 Hz), 3.26 (dd, 1H, H-3, *J* 7.5 Hz, *J* 4.5 Hz), 3.77 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 4.77 (dd, 1H, H-4, *J* 7.5 Hz, *J* 6.0 Hz), 4.92 (d, 1H, H-5, *J* 6.0 Hz), 7.20 (dd, 2H, H-11 and H-15, *J* 7.5 Hz, *J* 1.5 Hz),7.41-7.48 (m, 3H, H-12, H-13 and H-14). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 18.2 (C-17 or C-18), 19.5 (C-18 or C-17), 19.9 (C-8), 27.6 (C-16), 28.5 (C-7), 40.6 (C-6), 53.0 (C-3), 64.5 (C-5), 88.6 (C-4), 126.8 (C-11 and C-15), 129.4 (C-13), 129.5 (C-12 and C-14), 136.9 (C-

10), 171.1 (C-2). ***m/z*** (ES+) 327 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{24}N_2O_3Na^+$) requires ***m/z*** 327.1679, found ***m/z*** 327.1678.

A.2.7.21. 1-Butyl-3-isopropyl-4-nitro-5-pentylpyrrolidin-2-one 193nad

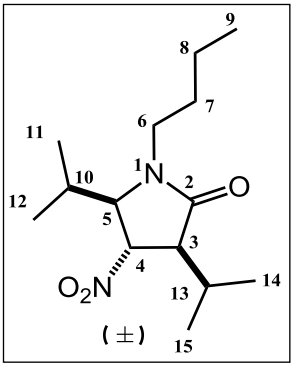


Prepared according to the general procedure **C** with methyl 3-methyl-2-(nitromethyl)butanoate **194d**, butylamine **167a** and hexanal **166n**. **193nad** (130 mg, 70% yield) was obtained as a separable mixture of two diastereoisomers (dr 23:1). The major diastereoisomer was isolated by flash column chromatography (petroleum ether / diethyl ether 4:1, R_{fmajor} = 0.16) as a yellow oil.

IR (cm^{-1}) ν_{max} 1697 (C=O), 1557 (NO_2), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.88-0.98 (m, 9H, H-9, H-14 and H-16 or H-17), 1.03 (d, 3H, H-17 or H-16, *J* 7.0 Hz), 1.24-1.40 (m, 8H, H-8, H-11, H-12 and H-13), 1.41-1.58 (m, 3H, H-7, H-10), 1.84-1.94 (m, 1H, H-10'), 2.34-2.43 (m, 1H, H-15), 2.91 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.08 (dd, 1H, H-3, *J* 6.5 Hz, *J* 5.0 Hz), 3.70 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.0 Hz), 3.91 (ddd, 1H, H-5, *J* 8.5 Hz *J* 5.0 Hz, *J* 3.5 Hz), 4.67 (app t, 1H, H-4, *J* 5.0 Hz). **^{13}C NMR**($CDCl_3$, 125 MHz) δ_C 13.7 (C-9 or C-14), 13.9 (C-14 or C-9), 18.2 (C-16 or C-17), 19.8 (C-17 or C-16), 20.0 (C-8 or C-11 or C-12 or C-13), 22.4 (C-11 or C-12 or C-13 or C-8), 23.5 (C-12 or C-13 or C-8 or C-11), 27.7 (C-15), 29.0 (C-7), 31.5 (C-13 or C-8 or C-11 or C-12), 31.7 (C-10), 40.2 (C-6), 53.7 (C-3), 60.1 (C-5), 85.0 (C-4), 170.7 (C-2). ***m/z*** (ES+) 321 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{30}N_2O_3Na^+$) requires ***m/z*** 321.2149, found ***m/z*** 321.2142.

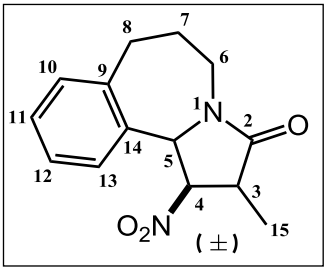
A.2.7.22. 1-Butyl-3,5-diisopropyl-4-nitropyrrolidinon-2-one 193aad

Prepared according to the general procedure **A** with methyl 3-methyl-2-(nitromethyl)butanoate **194d**, butylamine **167a** and isobutyraldehyde **166a**. **2p** (108 mg, 70% yield) was obtained as a separable mixture of two diastereoisomers (dr 30:1). The major diastereoisomer was isolated by flash column chromatography (gradient from petroleum ether / ethyl acetate 8:1 to 1:1, R_{fmajor} = 0.53 in petroleum ether /ethyl acetate 4:1) as a yellow oil.



IR (cm^{-1}) ν_{max} 1698 (C=O), 1558 (NO_2), 1372 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.84 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.93-0.98 (m, 6H, H-9 and H-14 or H-15), 1.01 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 1.04 (d, 3H, H-15 or H-14, *J* 7.0 Hz), 1.27-1.43 (m, 2H, H-8), 1.44-1.59 (m, 2H, H-7), 2.25 (septd, 1H, H-10, *J* 7.0 Hz, *J* 4.0 Hz), 2.39 (septd, 1H, H-13, *J* 7.0 Hz, *J* 4.5 Hz), 2.79 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.03 (dd, 1H, H-3, *J* 7.5 Hz, *J* 4.5 Hz), 3.84 (dt, 1H, H-6', *J* 14.0 Hz, *J* 8.5 Hz), 3.96 (dd, 1H, H-5, *J* 6.0 Hz, *J* 4.0 Hz), 4.83 (dd, 1H, H-4, J 7. 5 Hz, J 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 14.8 (C-11 or C-12), 17.6 (C-12 or C-11), 18.3 (C-14 or C-15), 19.6 (C-15 or C-14), 20.0 (C-8), 27.5 (C-10), 27.8 (C-13), 28.6 (C-7), 40.0 (C-6), 54.1 (C-3), 64.0 (C-5), 81.5 (C-4), 170.8 (C-2). ***m/z*** (ES+) 271 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{26}N_2O_3Na^+$) requires ***m/z*** 293.1836, found ***m/z*** 293.1830.

A.2.8. 2-methyl-1-nitro-1,2,5,6,7,11b-hexahydro-3H-pyrrolo[2,1-a][2]benzazepin-3-one 197dc



Prepared according to the general procedure **C** with 2-methyl-3-nitropropanoate **194c** (100 mg). **197dc** (100 mg, 59%) was obtained as an unseparable mixture of three diastereoisomers (dr 5: 3.5:1) after purification by flash column chromatography (gradient petroleum ether / ethyl acetate from 5:1 to 1:1): R_f= 0.12 in petroleum ether /ethyl acetate 5:1).

Data common to the 3 diastereoisomers

IR (cm^{-1}) ν_{max} 1699 (C=O), 1554 (NO_2), 1493 (C=C aromatic), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.06-7.32 (m, 4H, H-Ar). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 126.0 (C_{Ar}-H), 126.9 (C_{Ar}-H), 127.1 (C_{Ar}-H), 127.5 (C_{Ar}-H), 128.1 (C_{Ar}-H), 128.4 (C_{Ar}-H), 128.9 (C_{Ar}-H), 129.2 (C_{Ar}-H), 129.5 (C_{Ar}-H), 131.2 (C_{Ar}-H), 131.2 (C_{Ar}-H), 131.4 (C_{Ar}-H). ***m/z*** (ES-) 259 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}N_2O_3^+$) requires ***m/z*** 261.1234, found ***m/z*** 261.1233.

Major diastereomer 1

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.24 (d, 3H, H-15, *J* 7.5 Hz), 1.79-1.89 (m, 1H, H-7), 1.90-2.00 (m, 1H, H-7'), 2.79-2.83 (m, 1H, H-8), 2.85-2.88 (m, 1H, H-8'), 3.02-3.14 (m, 2H, H-3 and H-6), 4.29 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 6.5 Hz, *J* 3.5 Hz), 5.32 (d, 1H, H-5, *J* 3.0 Hz), 5.51 (dd, 1H, H-4, *J* 7.5 Hz, *J* 3.0 Hz).**^{13}C**

NMR ($CDCl_3$, 125 MHz) δ_C 10.2 (C-15), 25.9 (C-7), 32.2 (C-8), 39.5 (C-3), 41.5 (C-6), 65.8 (C-5), 88.2 (C-4), 134.8 (C-14), 140.4 (C-9), 171.2 (C-2).

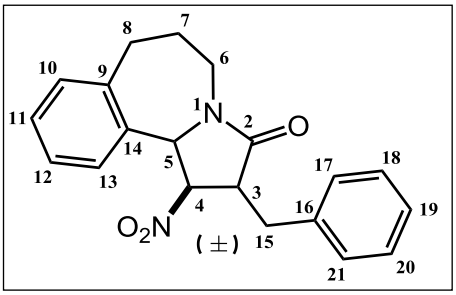
Diastereoisomer 2

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.39 (d, 3H, H-15, *J* 7.5 Hz), 1.63-1.76 (m, 1H, H-7), 2.19-2.24 (m, 1H, H-7'), 2.60 (ddd, 1H, H-8, *J* 14.5 Hz, *J* 5.0 Hz, *J* 3.0 Hz), 2.73-2.78 (m, 1H, H-8'), 2.89-2.97 (m, 1H, H-6), 3.22-3.31 (m, 1H, H-3), 4.03 (dd, 1H, H-6', *J* 14.5 Hz, *J* 8.0 Hz, *J* 1.5 Hz), 4.76 (dd, 1H, H-4, *J* 9.0 Hz, *J* 8.0 Hz), 5.26 (d, 1H, H-5, *J* 8.0 Hz).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.1 (C-15), 24.7 (C-7), 29.8 (C-8), 38.0 (C-6), 42.7 (C-3), 63.5 (C-5), 92.4 (C-4), 134.0 (C-14), 137.8 (C-9), 170.5 (C-2).

Minor Diastereoisomer 3

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.42 (d, 3H, H-15, *J* 8.0 Hz), 1.70-1.77 (m, 1H, H-7), 2.25-2.33 (m, 1H, H-7'), 2.40-2.46 (m, 1H, H-8), 2.91-2.96 (m, 1H, H-6), 3.13-3.21 (m, 1H, H-8'), 4.07-4.14 (m, 1H, H-6'), 5.11 (dd, 1H, H-4, *J* 7.5 Hz, *J* 2.0 Hz), 5.34 (d, 1H, H-5, *J* 7.5 Hz).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-15), 25.2 (C-7), 29.6 (C-8), 38.3 (C-6), 42.2 (C-3), 66.4 (C-5), 90.2 (C-4), 131.8 (C-14), 139.6 (C-9), 173.4 (C-2).

A.2.9. 2-Benzyl-1-nitro-1,2,5,6,7,11b-hexahydro-3H-pyrrolo[2,1-a][2]benzazepin-3-one 197da



Prepared according to the general procedure **C** with 2-benzyl-3-nitropropanoate **194a** (100 mg). **197da** (106 mg, 75%) was obtained as an unseparable mixture of three diastereoisomers (dr 2:1.6:1). The purification was achieved by flash column chromatography (petroleum ether / ethyl acetate 5:1) enabled to separate the major diasteroisomer from a mixture of the two minor ones: $R_{fminors}$ = 0.16 and R_{fmajor} = 0.04 in petroleum ether /ethyl acetate 5:1).

Major diastereomer 1

IR (cm^{-1}) ν_{max} 1695 (C=O), 1557 (NO_2), 1496 (C=C aromatic), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.69 (tdd, 2H, H-7, *J* 13.0 Hz, *J* 8.0 Hz, *J* 5.0 Hz), 2.22-2.35 (m, 1H, H-7'), 2.47 (ddd, 1H, H-8, *J* 14.0 Hz, *J* 5.0 Hz, *J* 2.0 Hz), 2. 71 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 10.0 Hz, *J* 8.0 Hz), 3.08-3.25 (m, 3H, H-8' and H-15), 3.56-3.62 (m, 1H, H-3), 4.07-4.16 (m, 1H, H-6'), 4.53 (d, 1H, H-5, *J* 7.5 Hz), 5.14 (dd, 1H, H-4, *J* 7.5 Hz, *J*

1.5 Hz), 6.92-6.97 (m, 1H, H-Ar), 7.03-7.07 (m, 1H, H-Ar), 7.16-7.20 (m, 2H, H-Ar), 7.22-7.26 (m, 2H, H-Ar), 7.26-7.31 (m, 1H, H-Ar), 7.32-7.37 (m, 2H, H-Ar). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.1 (C-7), 29.6 (C-8), 35.1 (C-15), 38.2 (C-6), 48.5 (C-3), 66.9 (C-5), 87.8 (C-4), 126.8 (C-Ar), 127.6 (C-Ar), 128.5 (C-Ar), 128.9 (C-Ar), 129.0 (C-Ar), 129.1 (C-Ar), 131.3 (C-Ar), 131.8 (C-Ar), 136.3 (C-Ar), 139.4 (C-Ar), 172.2 (C-2). ***m/z*** (ES-) 335 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{20}N_2O_3Na^+$) requires ***m/z*** 359.1366, found ***m/z*** 359.1364.

Data common to the mixture of minor diastereomers 2 and 3

IR ν_{max} 1702 cm^{-1} (C=O), 1556 cm^{-1} (NO_2), 1495 cm^{-1} (C=C aromatic), 1370 cm^{-1} (NO_2)1695 cm^{-1} (C=O), 1557 cm^{-1} (NO_2), 1496 cm^{-1} (C=C aromatic), 1368 cm^{-1} (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 6.99 (d, 1H, H_{Ar}), 7.02-7.09 (m, 2H, H_A), 7.15-7.30 (m, 13H, H_A), 7.31-7.36 (m, 2H, H_A). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 125.1 (C-Ar), 126.9 (C-Ar), 127.0 (C-Ar), 127.3 (C-Ar), 128.3 (C-Ar). ***m/z*** (ES-) 335 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{20}N_2O_3Na^+$) requires ***m/z*** 359.1366, found ***m/z*** 359.1365.

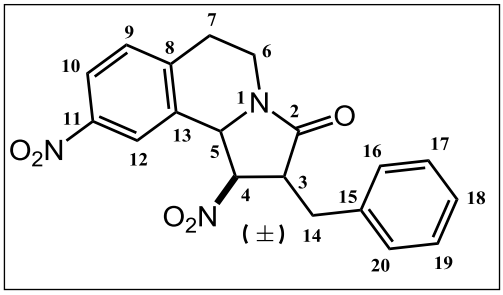
Data extracted for minor 2

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.82-1.97 (m, 2H, H-7), 2.65 (dd, 1H, H-15, *J* 15.0 Hz, *J* 10.5 Hz), 2.78-2.95 (m, 1H, H-8), 3.10-2.17 (m, 1H, H-6), 3.22-3.28 (m, 1H, H-3), 3.45 (dd, 1H, H-15', *J* 15.0 Hz, *J* 4.0 Hz), 4.45 (dt, 1H, H-6, *J* 13.5 Hz, *J* 5.0 Hz), 5.12 (s, 1H, H-5), 5.48 (d, 1H, H-4, *J* 6.5 Hz).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 26.4 (C-7), 31.2 (C-15), 33.1 (C-8), 42.9 (C-6), 46.3 (C-3), 64.0 (C-5), 86.9 (C-4), 134.8 (C-14), 170.2 (C-2).

Data extracted for minor 3

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.52-1.63 (m, 1H, H-7), 2.00-2.12 (m, 1H, H-7'), 2.23-2.31 (m, 1H, H-8), 2.78-2.96 (m, 1H, H-6), 3.08-3.12 (m, 1H, H-15), 3.31 (dd, 1H, H-15', *J* 14.0 Hz, *J*5.5 Hz), 3.58-3.66 (m, 1H, H-3), 4.04-4.16 (m, 1H, H-6'), 4.83 (t, 1H, H-4, *J* 8.0 Hz), 5.20 (d, 1H, H-5, *J* 8.0 Hz).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 24.8 (C-7), 29.1 (C-8), 33.3 (C-15), 38.0 (C-6), 48.9 (C-3), 65.9 (C-5), 88.1 (C-4), 133.9 (C-14), 136.0 (C-16), 169.0 (C-2).

A.2.10. 2-Benzyl-1,9-dinitro-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one 197ba



Prepared according to the general procedure **C** with 2-benzyl-3-nitropropanoate **194a** (100 mg). **197ba** (160 mg, 90%) was obtained as an unseparable mixture of three diastereoisomers (dr 2.8:1.1:1). The purification was achieved by flash column chromatography (petroleum ether / ethyl acetate 2:1 then ethyl acetate/MeOH 10:1)

Data extracted for the major diastereoisomer

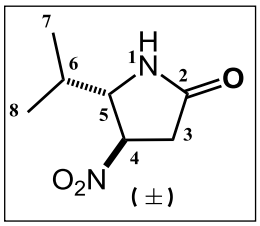
IR (cm^{-1}) ν_{max} 1701 (C=O), 1589 (C=C aromatic), 1556 (NO_2), 1522 (NO_2), 1495 (C=C aromatic), 1347 (NO_2).**^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.69 (tdd, 2H, H-7, *J* 13.0 Hz, *J* 8.0 Hz, *J* 5.0 Hz), 2.22-2.35 (m, 1H, H-7'), 2.47 (ddd, 1H, H-8, *J* 14.0 Hz, *J* 5.0 Hz, *J* 2.0 Hz), 2. 71 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 10.0 Hz, *J* 8.0 Hz), 3.08-3.25 (m, 3H, H-8 and H-15), 3.56-3.62 (m, 1H, H-3), 4.07-4.16 (m, 1H, H-6), 4.53 (d, 1H, H-5, *J* 7.5 Hz), 5.14 (dd, 1H, H-4, *J* 7.5 Hz, *J* 1.5 Hz), 6.92-6.97 (m, 1H, H-Ar), 7.03-7.07 (m, 1H, H-Ar), 7.16-7.20 (m, 2H, H-Ar), 7.22-7.26 (m, 2H, H-Ar), 7.26-7.31 (m, 1H, H-Ar), 7.32-7.37 (m, 2H, H-Ar). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 25.1 (C-7), 29.6 (C-8), 35.1 (C-15), 38.2 (C-6), 48.5 (C-3), 66.9 (C-5), 87.8 (C-4), 126.8 (C-Ar), 127.6 (C-Ar), 128.5 (C-Ar), 128.9 (C-Ar), 129.0 (C-Ar), 129.1 (C-Ar), 131.3 (C-Ar), 131.8 (C-Ar), 136.3 (C-Ar), 139.4 (C-Ar), 172.2 (C-2). ***m/z*** (ES-) 335 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{20}N_2O_3Na^+$) requires ***m/z*** 359.1366, found ***m/z*** 359.1364.

In order to easily compare the relative stereochemistry of the various pyrrolidinones above, the values of the coupling constants between H_3/H_4 and H_4/H_5, are summarised in the following table.

Compound	**diastereoisomer**	***J* H_3-H_4**	***J* H_4-H_5**
193aaa	major	6.0 Hz	5.5 Hz
	minor	7.5 Hz	< 1.0 Hz
193aab	major	5.0 Hz	5.0 Hz
	minor	8.5 Hz	< 1.0 Hz
193aac	major	5.0 Hz	5.0 Hz
	minor	8.5 Hz	< 1.0 Hz
193afa	major	7.0 Hz	6.0 Hz
	minor	7.5 Hz	< 1.0 Hz
193afb	major	5.0 Hz	5.0 Hz
	minor	8.0 Hz	1.5 Hz
193afc	major	-	5.5 Hz
	minor	9.0 Hz	1.5 Hz
193baa	major	7.5 Hz	5.5 Hz
193bab	major	7.5 Hz	5.5 Hz
193bac	major	7.5 Hz	6.0 Hz
	minor	8.0 Hz	1.5 Hz
193faa	major	5.5 Hz	5.5 Hz
193gaa	major	7.0 Hz	6.0 Hz
193oaa	major	7.0 Hz	5.5 Hz
193eaa	major	7.5 Hz	5.0 Hz
193aba	major	6.5 Hz	5.5 Hz
	minor	7.5 Hz	4.0 Hz
193nac	major	7.0 Hz	5.5 Hz
	minor	7.5 Hz	1.5 Hz
196	major	6.0 Hz	4.5 Hz
193nmc	major	6.5 Hz	5.5 Hz
	minor	7.5 Hz	2.0 Hz
193amc	major	5.0 Hz	4.0 Hz
193rad	major	7.5 Hz	4.5 Hz
193bad	major	8.0 Hz	6.0 Hz
193sad	major	multiplet	multiplet

A.3 Experimental- Chapter 3

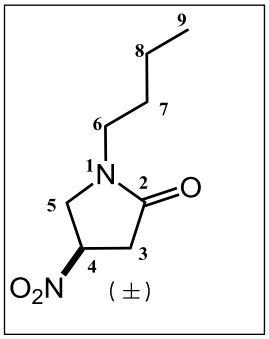
A.3.1. 5-isopropyl-4-nitropyrrolidin-2-one 198a



A 50mL, one-necked flask, equipped with a rubber seal and a magnetic stirrer bar was charged with methyl 3-nitropropanoate (1.0 g, 7.5 mmol, 1.0 eq), isobutyraldehyde (1.1 mL, 11.3 mmol, 1.5 eq), ammonium acetate (0.9 g, 11.3 mmol, 1.5 eq), benzoic acid (4.6 g, 37.5 mmol, 5.0 eq) and methanol (30 mL). The reaction mixture was purged three times with N_2 and stirred at 55 °C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate. The reaction mixture was concentrated under vacuum and the residue taken up in dichloromethane. The organic layer was washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and dichloromethane was removed under vacuum. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether 1:1, R_f = 0.2). 5-Isopropyl-4-nitropyrrolidin-2-one **198a** was isolated in 47% yield (0.6 g) as a yellow oil.

IR (cm^{-1}) ν_{max} 3150-3300 (NH_2), 1702 (C=O), 1555 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.00-1.04 (m, 6H, H-7 and H-8), 1.73 (br s, 1H, N-H), 1.82-1.97 (m, 1H, H-6), 2.84 (dd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz), 3.06 (dd, 1H, H-3', *J* 18.5 Hz, *J* 3.0 Hz), 3.90 (ddd, 1H, H-5, *J* 6.0 Hz, *J* 3.0 Hz, *J* 1.0 Hz), 4.91 (dt, 1H, H-4, *J* 8.5 Hz, *J* 3.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 17.5 (C-7 or C-8), 18.1 (C-8 or C-7), 32.6 (C-6), 34.9 (C-3), 65.0 (C-5), 82.5 (C-4), 173.1 (C-2). ***m/z*** (ES+) 195 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{12}N_2O_3Na^+$) requires ***m/z*** 195.0740, found ***m/z*** 195.0744.

A.3.2. 1-Butyl-4-nitropyrrolidin-2-one 199a

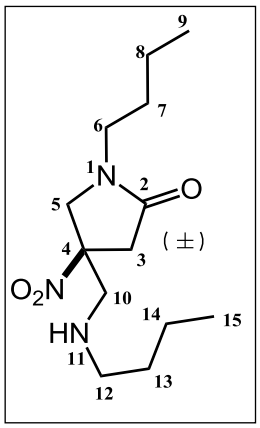


A 50 mL, one-necked flask, was charged with methyl 3-nitropropanoate (0.50 g, 3.75 mmol, 1 eq), formaldehyde (37% in water, 0.45 mL, 5.64 mmol, 1.5 eq), butylamine (0.56 mL, 5.64 mmol, 1.5 eq), benzoic acid (2.49 g, 18.75 mmol, 5.0 eq) and toluene (30 mL, 0.12 mol/L). The reaction mixture was purged three times with N_2 and stirred at 70 °C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate. The reaction mixture was concentrated under vacuum and the residue was taken up in dichloromethane. The organic layer was washed three times

with aqueous 1M K_2CO_3, dried over Na_2SO_4 and dichloromethane was removed under vacuum. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether 1:1, R_f = 0.5). 1-butyl-4-nitropyrrolidin-2-one **199a** was isolated in 75% yield (0.53 g) as a colorless oil.

IR (cm^{-1}) ν_{max} 1698 (C=O), 1555 (NO_2), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.94 (d, 3H, H-9, *J* 7.5 Hz), 1.28-1.38 (m, 2H, H-8), 1.48-1.56 (m, 2H, H-7), 2.94 (dd, 1H, H-3, *J* 18.0 Hz, *J* 8.5 Hz), 3.11 (dd, 1H, H-3', *J* 18.0 Hz, *J* 3.5 Hz), 3.21-3.29 (m, 1H, H-6), 3.36-3.44 (m, 1H, H-6'), 3.86 (dd, 1H, H-5, *J* 12.0 Hz, *J* 7.5 Hz), 3.97 (dd, 1H, H-5', *J* 12.0 Hz, *J* 2.5 Hz), 5.05-5.26 (m, 1H, H-4). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 11.6 (C-9), 19.9 (C-8), 29.0 (C-7), 36.0 (C-3), 42.1 (C-6), 50.6 (C-5), 77.2 (C-4), 169.4 (C-2). ***m/z*** (ES+) 185 ($[M-H]^-$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{14}N_2O_3Na^+$) requires ***m/z*** 209.0897, found ***m/z*** 209.0897.

A.3.3. 1-Butyl-4-[(butylamino)methyl]-4-nitropyrrolidin-2-one 203

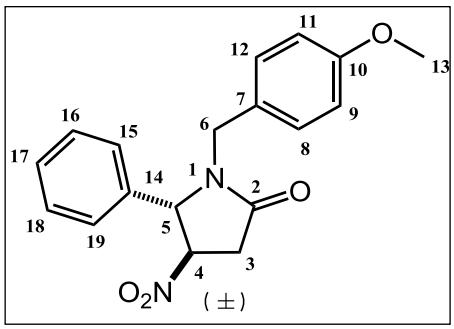


A 10mL, one-necked flask, was charged with methyl 3-nitropropanoate (100 mg, 0.75 mmol, 1.0 eq), paraformaldehyde (33 mg, 1.13 mmol, 1.5 eq), butylamine (113 µL, 1.13 mmol, 1.5 eq), benzoic acid (150 mg, 1.13 mmol, 1.5 eq) and tetrahydrofuran (3 mL, 0.25 mol/L). The reaction mixture was purged three times with N_2 and stirred at 65 °C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate. The reaction mixture was concentrated under vacuum and the residue was taken up in dichloromethane. The organic layer was washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and dichloromethane was removed under vacuum. The crude product was purified by flash column chromatography (dichloromethane/methanol 10:1, R_f = 0.2). 1-Butyl-4-[(butylamino)methyl]-4-nitropyrrolidin-2-one **203** was isolated in 65% yield (132 mg) as a brown oil.

IR (cm^{-1}) ν_{max} 3400 (broad, N-H), 1698 (C=O), 1549 (NO_2), 1314 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89 (t, 3H, H-9 or H-15, *J* 7.0 Hz), 0.92 (t, 3H, H-15 or H-9, *J* 7.5 Hz), 1.25-1.36 (m, 4H, H-8 and H-14), 1.35-1.45 (m, 2H, H-13), 1.47-1.57 (m, 2H, H-7), 1.7 (br s, 1H, N-H), 2.61 (td, 2H, H-12, *J* 7.0 Hz, *J* 3.5 Hz), 2.77 (d, 1H, H-3, *J* 18.0 Hz), 3.08 (d, 1H, H-10, *J* 13.5 Hz), 3.20 (d, 1H, H-3', *J* 18.0 Hz), 3.26 (d, 1H,

H-10', *J* 13.5 Hz), 3.21-3.40 (m, 2H, H-6), 3.65 (d, 1H, H-5, *J* 11.5 Hz), 4.05 (d, 1H, H-5', *J* 11.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9 or C-15), 13.9 (C-15 or C-9), 19.9 (C-8 or C-14), 20.1 (C-14 or C-8), 29.0 (C-7), 32.1 (C-13), 40.2 (C-3), 42.1 (C-6), 50.0 (C-12), 53.5 (C-5), 55.4 (C-10), 89.9 (C-4), 169.5 (C-2). ***m/z*** (ES+) 272 ($[M+H]^+$, 100%).

A.3.4. 1-(4-methoxybenzyl)-4-nitro-5-phenylpyrrolidin-2-one

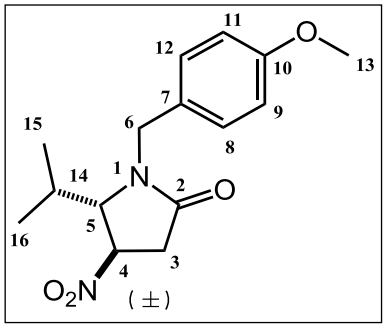


A 25 mL, one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl 3-nitropropanoate (1.0 g, 7.5 mmol, 1.0 eq), benzoic acid (1.4 g, 11.3 mmol, 1.5 eq) and toluene (15 mL). The reaction mixture was purged three times with N_2, then *p*-methoxybenzylamine (1.5 mL, 11.3 mmol, 1.5 eq) and benzaldehyde (1.1 mL, 11.3 mmol, 1.5 eq) were added *via* a syringe. The reaction was stirred at 70 ˚C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate. The reaction mixture was concentrated under vacuum and the residue was taken up in dichloromethane. The organic layer was washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether 1:1, R_f = 0.2). 1-(4-Methoxybenzyl)-4-nitro-5-phenylpyrrolidin-2-one was isolated in 74% yield (1.8 g) as a yellow oil.

IR (cm^{-1}) ν_{max} 1699 (C=O), 1611 (C=C aromatic), 1555 (NO_2), 1513 (aromatic C=C), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.11 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 1.0 Hz), 3.20 (dd, 1H, H-3', *J* 18.0 Hz, *J* 3.0 Hz), 3.49 (d, 1H, H-6, *J* 14.5 Hz), 3.80 (s, 3H, H-13), 4.81 (d, 1H, H-5, *J* 3.0 Hz), 4.89 (dt, 1H, H-4, *J* 8.0 Hz, *J* 3.0 Hz), 5.16 (d, 1H, H-6', *J* 14.5 Hz), 6.78-6.88 (m, 2H, H-9 and H-11), 7.00 (d, 2H, H-8 and H-12, *J* 8.5 Hz), 7.12-7.19 (m, 2H, H_{Ar}), 7.37-7.52 (m, 3H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 34.7 (C-3), 44.0 (C-6), 55.2 (C-13), 65.2 (C-5), 84.6 (C-4), 114.2 (C-9 and C-11), 126.4 (C-8 and C-12), 126.6 (C-7), 129.5 (C_{Ar}-H), 129.6 (2x C_{Ar}-H), 129.7 (2x C_{Ar}-H), 136.0 (C-14), 159.3 (C-10), 169.9 (C-2). ***m/z*** (ES+) 349 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{18}N_2O_4Na^+$) requires ***m/z*** 349.1159, found ***m/z*** 349.1147.

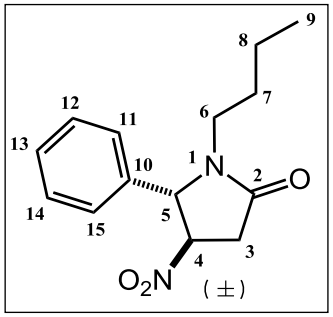
A.3.5. 5-isopropyl-1-(4-methoxybenzyl)-4-nitropyrrolidin-2-one

A 25 mL, one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl 3-nitropropanoate (1.0 g, 7.5 mmol, 1.0 eq), benzoic acid (1.4 g, 11.3 mmol, 1.5 eq) and toluene (15 mL). The reaction mixture was purged three times with N_2 , then *p*-methoxybenzylamine (1.5 mL, 11.3 mmol, 1.5 eq) and isobutyraldehyde (1.0 mL, 11.3 mmol, 1.5 eq) were added *via* a syringe. The reaction was stirred at 70 ˚C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate. The reaction mixture was concentrated under vacuum and the residue was taken up in dichloromethane. The organic layer was washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether 1:1, R_f = 0.1). 5-Isopropyl-1-(4-methoxybenzyl)-4-nitropyrrolidin-2-one was isolated in 91% yield (2.0 g) as a yellow oil.



IR (cm^{-1}) ν_{max} 1698 (C=O), 1556 (NO_2), 1513 (aromatic C=C), 1369 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.77 (d, 3H, H-15 or H-16, *J* 7.0 Hz), 1.01 (d, 3H, H-16 or H-15, *J* 7.0 Hz), 2.09-2.30 (m, 1H, H-14), 2.87 (ddd, 1H, H-3, *J* 18.5 Hz, *J* 8.5 Hz, *J* 1.0 Hz), 3.11 (dd, 1H, H-3', *J* 18.5 Hz, *J* 2.0 Hz), 3.70 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0 Hz), 3.80 (s, 3H, H-13), 3.84 (d, 1H, H-6, *J* 15.0 Hz), 4.84 (dt, 1H, H-4, *J* 8.5 Hz, *J* 2.0 Hz), 5.08 (d, 1H, H-6', *J* 15.0 Hz), 6.61-6.94 (m, 2H, H-9 and H-11), 7.05-7.19 (m, 2H, H-8 and H-12). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (C-15 or C-16), 18.1 (C-16 or C-15), 27.8 (C-14), 35.9 (C-3), 43.8 (C-6), 55.2 (C-13), 66.9 (C-5), 78.3 (C-4), 114.3 (C-9 and C-11), 126.8 (C-7), 129.2 (C-8 and C-12), 159.3 (C-10), 170.0 (C-2). ***m/z*** (ES+) 315 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}N_2O_4Na^+$) requires ***m/z*** 315.1315, found ***m/z*** 315.1308.

A.3.6. 1-Butyl-4-nitro-5-phenylpyrrolidin-2-one



A 25 mL, one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl 3-nitropropanoate (1.0 g, 7.5 mmol, 1.0 eq), benzoic acid (1.4 g, 11.3 mmol, 1.5 eq) and toluene (15 mL). The reaction mixture was purged three times with N_2 , then butylamine (1.1 mL, 11.3 mmol, 1.5 eq) and benzaldehyde (1.4 mL, 11.3 mmol, 1.5 eq) were added *via* a syringe. The reaction was stirred at 70 ˚C, under a N_2 atmosphere, until full consumption of methyl-3-nitropropanoate. The reaction mixture was concentrated under vacuum and the was residue taken up in dichloromethane. The organic layer was washed three times with aqueous 1M K_2CO_3, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether / diethyl ether 1:1, R_f = 0.2). 1-Butyl-4-nitro-5-phenylpyrrolidin-2-one was isolated in 87% yield (1.7 g) as an orange solid.

mp 87-90 ˚C. **IR** (cm^{-1}) ν_{max} 1698 (C=O), 1556 (NO_2), 1496 (aromatic C=C), 1367 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.89 (t, 3H, H-9, *J* 7.5 Hz), 1.15-1.38 (m, 2H, H-8), 1.46 (quint, 2H, H-7, *J* 7.0 Hz), 2.64 (dt, 1H, H-6, *J* 13.5 Hz, *J* 7.0 Hz), 3.04 (ddd, 1H, H-3, *J* 18.0 Hz, *J* 8.0 Hz, *J* 1.0 Hz), 3.15 (dd, 1H, H-3', *J* 18.0 Hz, *J* 2.5 Hz), 3.81 (dt, 1H, H-6', *J* 13.5 Hz, *J* 7.0 Hz), 4.88 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.5 Hz), 5.17 (d, 1H, H-5, *J* 2.5 Hz), 7.16-7.26 (m, 2H, H_{Ar}), 7.39-7.51 (m, 3H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.6 (C-9), 19.8 (C-8), 28.8 (C-7), 34.6 (C-3), 40.6 (C-6), 66.0 (C-5), 84.9 (C-4), 126.2 (2x C_{Ar}-H), 129.5 (C-13), 129.7 (2x C_{Ar}-H), 136.4 (C-10), 169.7 (C-2). ***m/z*** (ES+) 285 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}N_2O_3Na^+$) requires ***m/z*** 285.1210, found ***m/z*** 285.1209.

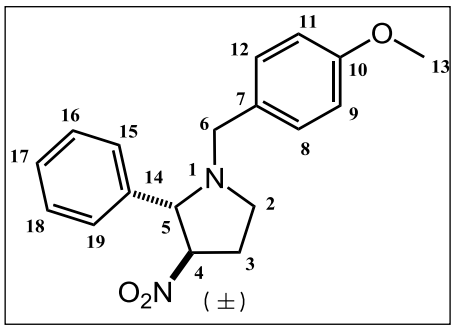
A.3.7. Reduction of the lactam carbonyl group: from pyrrolidinone to pyrrolidine 206

General procedure **D**: an oven-dried, one-necked flask, purged with nitrogen, equipped with a rubber seal and a magnetic stirrer bar was charged with dry tetrahydrofuran (0.34 mol/L), nitro-pyrrolidinone (1.0 eq), and sodium borohydride (2.6 eq). This was stirred at room temperature for 15 minutes, then BF_3.THF (2.9 eq) was added dropwise. The reaction was stirred for 3 hours at 40 ˚C, and then cooled to 0 ˚C. A 1:1 solution of tetrahydrofuran/water was then added dropwise, creating excess foaming. Water was added and tetrahydrofuran was removed under vacuum. The aqueous

layer was extracted three times with ethyl acetate. The combined organic layers were then dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by flash column chromatography.

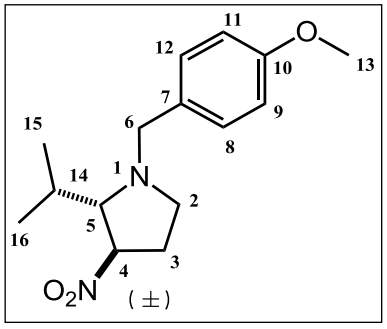
A.3.7.1. 1-(4-Methoxybenzyl)-3-nitro-2-phenylpyrrolidine 206a

Prepared according to the general procedure **D** with 1-(4-methoxybenzyl)-4-nitro-5-phenylpyrrolidin-2-one (1.7 g, 1.0 eq). 1-(4-Methoxybenzyl)-3-nitro-2-phenylpyrrolidine **206a** (0.5 g, 28% yield) was purified by flash column chromatography (petroleum ether/diethyl ether 5:1, R_f = 0.6).



IR (cm^{-1}) ν_{max} 1612 (C=C aromatic), 1556 (NO_2), 1493 (aromatic C=C), 1301 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 2.37-2.46 (m, 2H, H-3), 2.63 (dt, 1H, H-2, *J* 9.5 Hz, *J* 8.0 Hz), 3.09-3.13 (m, 1H, H-2'), 3.15 (d, 1H, H-6, *J* 13.0 Hz), 3.77 (d, 1H, H-6', *J* 13.0 Hz), 3.80 (s, 3H, H-13), 4.92 (d, 1H, H-5, *J* 6.5 Hz), 4.77-4.82 (m, 1H, H-4), 6.82-6.87 (m, 2H, H-9 and H-11), 7.15-7.19 (m, 2H, H-8 and H-12), 7.33-7.38 (m, 1H, H-17), 7.39-7.44 (m, 2H, H-16 and H-18), 7.46-7.51 (m, 2H, H-15 and H-19). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 29.4 (C-3), 51.4 (C-2), 55.2 (C-13), 56.4 (C-6), 73.9 (C-5), 92.3 (C-4), 113.6 (C-9 and C-11), 127.6 (C-15 and C-19), 128.5 (C-17), 128.9 (C-16 and C-18), 129.8 (C-8 and C-12), 130.2 (C-14), 139.1 (C-7), 157.9 (C-10). ***m/z*** (ES+) 335 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}N_2O_3Na^+$) requires ***m/z*** 335.1366, found ***m/z*** 335.1364.

A.3.7.2. 2-Isopropyl-1-(4-methoxybenzyl)-3-nitropyrrolidine 206b

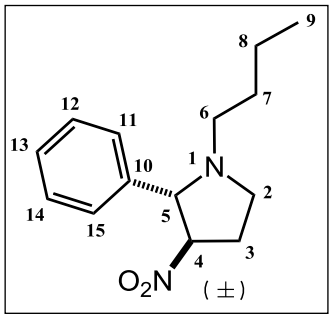


Prepared according to the general procedure **D** with 5-isopropyl-1-(4-methoxybenzyl)-4-nitropyrrolidin-2-one (1.6 g, 1.0 eq). 2-Isopropyl-1-(4-methoxybenzyl)-3-nitropyrrolidine **206b** (0.5 g, 33% yield) was purified by flash column chromatography (petroleum ether/diethyl ether 10:1, R_f = 0.8).

IR (cm^{-1}) ν_{max} 1612 (aromatic C=C), 1549 (NO_2), 1511 (aromatic C=C), 1368 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.97 (d, 3H, H-15 or H-16, *J* 7.0 Hz), 1.02 (d, 3H, H-16 or H-15, *J* 7.0 Hz), 1.95-2.02 (m, 1H, H-

14), 2.03-2.12 (m, 1H, H-3), 2.24-2.30 (m, 1H, H-3'), 2.64 (ddd, 1H, H-2, *J* 11.5 Hz, *J* 9.0 Hz, *J* 6.0 Hz), 2.92-2.99 (m, 1H, H-2'), 3.05 (t, 1H, H-5, *J* 4.0 Hz), 3.37 (d, 1H, H-6, *J* 13.0 Hz), 3.81 (s, 3H, H-13), 3.96 (d, 1H, H-6', *J* 13.0 Hz), 4.77 (ddd, 1H, H-4, *J* 8.0 Hz, *J* 4.0 Hz, *J* 1.5 Hz), 6.84-6.88 (m, 2H, H-9 and H-11), 7.21-7.26 (m, 2H, H-8 and H-12). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 16.2 (C-15 or C-16), 19.3 (C-16 or C-15), 29.3 (C-14), 31.2 (C-3), 52.4 (C-2), 55.2 (C-13), 58.0 (C-6), 74.5 (C-5), 86.8 (C-4), 113.6 (C-9 and C-11), 129.6 (C-8 and C-12), 131.4 (C-7), 158.7 (C-10). ***m/z*** (ES+) 279 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N_2O_3^+$) requires ***m/z*** 279.1703, found ***m/z*** 279.1700.

A.3.7.3. 1-Butyl-3-nitro-2-phenylpyrrolidine 206c



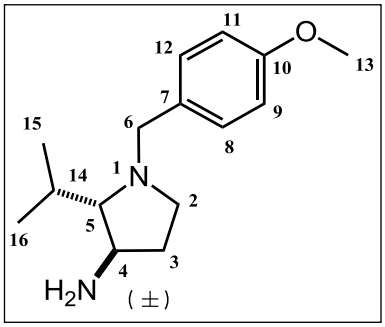
Prepared according to the general procedure **D** with 1-butyl-4-nitro-5-phenylpyrrolidin-2-one (1.6 g, 1.0 eq). 1-Butyl-3-nitro-2-phenylpyrrolidin-2-one **206c** (0.5 g, 33% yield) was purified by flash column chromatography (petroleum ether/diethyl ether 10: 1, R_f = 0.8). **IR** (cm^{-1}) ν_{max} 1602 (NO_2), 1493 (aromatic C=C), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.84 (t, 3H, H-9, *J* 7.5 Hz), 1.17-1.28 (m, 1H, H-8), 1.30-1.34 (m, 1H, H-8'), 1.37-1.47 (m, 2H, H-7), 2.19 (ddd, 1H, H-6, *J* 12.0 Hz, *J* 7.5 Hz, *J* 5.0 Hz), 2.42-2.48 (m, 2H, H-3), 2.53 (dt, 1H, H-6', *J* 12.0 Hz, *J* 8.0 Hz), 2.59-2.66 (m, 1H, H-2), 3.39 (ddd, 1H, H-2', *J* 9.0 Hz, *J* 7.0 Hz, *J* 2.0 Hz), 3.79 (d, 1H, H-5, *J* 6.0 Hz), 4.74 (ddd, 1H, H-4, *J* 8.5 Hz, *J* 6.0 Hz, *J* 4.5 Hz), 7.21-7.56 (m, 5H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.9 (C-9), 20.3 (C-8), 29.6 (C-3), 30.3 (C-7), 51.7 (C-2), 53.1 (C-6), 74.7 (C-5), 92.4 (C-4), 127.5 (C-11 and C-15), 128.3 (C-13), 128.7 (C-12 and C-14), 139.7 (C-10). ***m/z*** (ES+) 249 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}N_2O_2^+$) requires ***m/z*** 249.1598, found ***m/z*** 249.1597.

A.3.8. Reduction of the nitro group to the corresponding amine 207

General procedure **E**: a one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with nitro-pyrrole (1.0 eq), ethanol (0.2 mol/L) and nickel chloride hexahydrate (1.0 eq). This was cooled to 0 ˚C and sodium borohydride (11.0 eq) was added portionwise. The reaction was stirred for 2 hours at 0 ˚C. The reaction mixture was then quenched with a saturated solution of

aqueous ammonium chloride. The aqueous layer was extracted three times with chloroform. The combined organic layers were then dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by flash column chromatography.

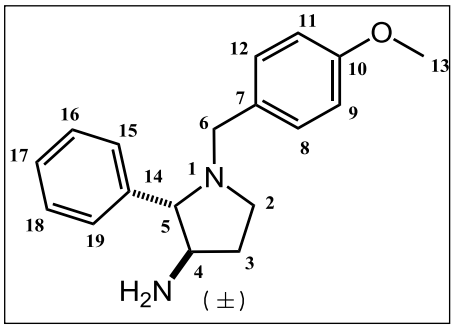
A.3.8.1. 2-Isopropyl-1-(4-methoxybenzyl)pyrrolidin-3-amine 207a



Prepared according to the general procedure **E** with 2-isopropyl-1-(4-methoxybenzyl)-3-nitropyrrolidine **206a** (500 mg, 1.0 eq). 2-Isopropyl-1-(4-methoxybenzyl)pyrrolidin-3-amine **207a** (367 mg, 82% yield) was purified by flash column chromatography (eluent from dichloromethane / methanol 5:1 to 1:1 , (R_f = 0.3 dichloromethane / methanol 1:1).

IR (cm^{-1}) ν_{max} 1612 (aromatic C=C), 1464 (aromatic C=C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.96 (d, 3H, H-15 or H-16, *J* 7.0 Hz), 1.05 (d, 3H, H-16 or H-15, *J* 7.0 Hz), 1.56 (dd, 1H, H-3, *J* 13.0 Hz, *J* 6.5 Hz), 1.86-2.00 (m, 2H, H-3' and H-14), 2.24 (t, 1H, H-5, *J* 3.5 Hz), 2.44-2.53 (m, 1H, H-2), 2.85 (t, 1H, H-2', *J* 8.0 Hz), 3.10 (br s, 2H, NH_2), 3.32 (d, 1H, H-6, *J* 13.0 Hz), 3.37 (ddd, 1H, H-4, *J* 6.5 Hz, *J* 3.5 Hz, *J* 1.0 Hz),3.80 (s, 3H, H-13), 3.95 (d, 1H, H-6', *J* 13.0 Hz), 6.84 (d, 2H, H-9 and H-11, *J* 8.5 Hz), 7.24 (m, 2H, H-8 and H-12, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 17.0 (C-15 or C-16), 19.9 (C-16 or C-15), 29.1 (C-14), 33.3 (C-3), 51.6 (C-2), 52.3 (C-4), 55.2 (C-13), 58.5 (C-6), 78.0 (C-5), 113.5 (C-9 and C-11), 129.7 (C-8 and C-12), 132.6 (C-7), 158.5 (C-10). ***m/z*** (ES+) 249 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{25}N_2O^+$) requires ***m/z*** 249.1961, found ***m/z*** 249.1967.

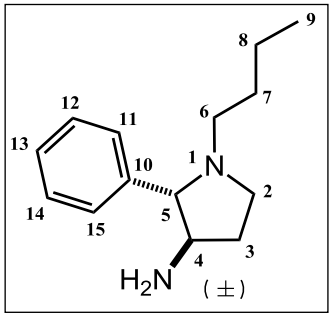
A.3.8.2. 1-(4-Methoxybenzyl)-2-phenylpyrrolidin-3-amine 207b



Prepared according to the general procedure **E** with 1-(4-methoxybenzyl)-3-nitro-2-phenylpyrrolidine **206b** (250 mg, 1.0 eq). 1-(4-methoxybenzyl)-2-phenylpyrrolidin-3-amine **207b** (133 mg, 60% yield) was purified by flash column chromatography (dichloromethane / methanol 10:1.5, R_f = 0.5).

IR (cm^{-1}) ν_{max} 1612 (C=C aromatic), 1492 (aromatic C=C), 1247 (C-O-C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.55 (dddd, 1H, H-3, *J* 13.0 Hz, *J* 9.5 Hz *J* 6.5 Hz, *J* 3.5 Hz), 2.00 (br s, 2H, NH_2), 2.27 (dq, 1H, H-3', *J* 13.0 Hz, *J* 8.5 Hz), 2.39-2.47 (m, 1H, H-2), 2.97-3.05 (m, 2H, H-5 and H-6), 3.06-3.12 (m, 1H, H-2'), 3.20-3.28 (m, 1H, H-4), 3.73 (d, 1H, H-6', *J* 13.0 Hz), 3.79 (s, 3H, H-13), 6.83 (d, 2H, H-9 and H-11, *J* 8.5 Hz), 7.17 (d, 2H, H-8 and H-12, *J* 8.5 Hz), 7.29-7.34 (m, 1H, H-17), 7.39 (t, 2H, H-16 and H-18, *J* 7.5 Hz), 7.49 (d, 2H, H-15 and H-19, *J* 7.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 31.9 (C-3), 50.9 (C-2), 55.2 (C-13), 57.2 (C-6), 60.4 (C-4), 78.7 (C-5), 113.5 (C-9 and C-11), 127.6 (C-17), 127.8 (C-15 and C-19), 128.7 (C-16 and C-18), 129.8 (C-8 and C-12), 131.5 (C-7), 141.4 (C-14), 158.3 (C-10). ***m/z*** (ES+) 283 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{23}N_2O^+$) requires ***m/z*** 283.1805, found ***m/z*** 283.1809.

A.3.8.3. 1-Butyl-2-phenylpyrrolidin-3-amine 207c

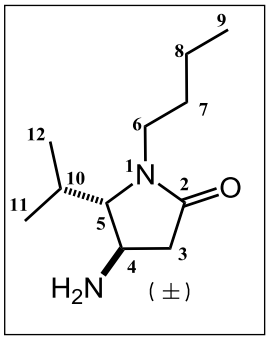


Prepared according to the general procedure **E** with 1-butyl-3-nitro-2-phenylpyrrolidine **206c** (250 mg, 1.0 eq). 1-Butyl-2-phenylpyrrolidin-3-amine **207c** (165 mg, 76% yield) was purified by flash column chromatography (dichloromethane / methanol 10:1.5, R_f = 0.4).

IR (cm^{-1}) ν_{max} 1492 (aromatic C=C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.82 (t, 3H, H-9, *J* 7.5 Hz), 1.15-1.24 (m, 1H, H-8), 1.24-1.33 (m, 1H, H-8'), 1.34-1.43 (m, 2H, H-7), 1.56 (dddd, 1H, H-3, *J* 13.0 Hz, *J* 9.5 Hz, *J* 6.5 Hz, *J* 3.5 Hz), 1.70 (br s, 2H, NH_2), 2.00 (ddd, 1H, H-6, *J* 12.0 Hz, *J* 7.5 Hz, *J* 5.5 Hz), 2.31 (dq, 1H, H-3', *J* 13.0 Hz, *J* 8.5 Hz), 2.36-2.44 (m, 1H, H-2), 2.44-2.53 (m, 1H, H-6'), 2.83 (d, 1H, H-5, *J* 8.0 Hz), 3.15-3.22 (m, 1H, H-4), 3.34 (td, 1H, H-2', *J* 9.0 Hz, *J* 3.5 Hz), 7.26-7.30 (m, 2H, H_{Ar}), 7.31-7.41 (m, 3H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.0 (C-9), 20.5 (C-8), 30.2 (C-7), 32.1 (C-3), 51.3 (C-2), 54.1 (C-6), 60.3 (C-4), 79.9 (C-5), 127.4 (C-13), 127.7 (2x C_{Ar}-H), 128.5 (2x C_{Ar}-H), 142.3 (C-10). ***m/z*** (ES+) 219 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}N_2^+$) requires ***m/z*** 219.1856, found ***m/z*** 219.1858.

A.3.9. 4-Amino-1-butyl-5-isopropylpyrrolidin-2-one 208

A 10 mL, one-neck flask, was charged with 1-butyl-5-isopropyl-4-nitropyrrolidin-2-one **173aa** (50 mg, 0.22 mmol, 1 eq), ethanol (1 mL) and nickel(II) chloride hexahydrate (52 mg, 0.22 mmol, 1 eq). The mixture was stirred at 0 ˚C and sodium borohydride (91.5 mg, 2.42 mmol, 11 eq) was added portionwise. The mixture was then stirred at 0 ˚C for 2 hours. The reaction was then quenched with an aqueous ammonium chloride solution (5 mL) and diluted with chloroform (5 mL). The layers were separated and the aqueous layer was extracted twice with chloroform, dired over magnesium sulphate, filtered through celite and concentrated under vacuum to afford 35 mg (80% yield) of desired amine **208**.

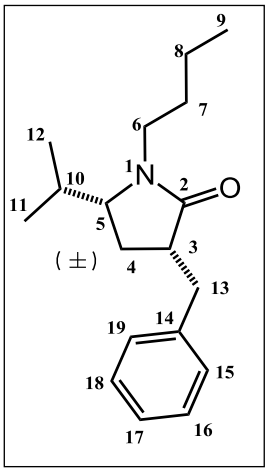


IR (cm^{-1}) ν_{max} 1667 (C=O). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.72 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.89 (t, 3H, H-9, *J* 7.5 Hz), 1.00 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 1.24-1.36 (m, 2H, H-8), 1.38-1.59 (m, 4H, H-7 and N-H), 1.97-2.05 (m, 1H, H-10), 2.04 (dd, 1H, H-3, *J* 17.5 Hz, *J* 2.0 Hz), 2.64 (dd, 1H, H-3', *J* 17.5 Hz, *J* 8.0 Hz), 2.78 (ddd, 1H, H-6, *J* 14.0 Hz, *J* 9.0 Hz, *J* 5.0 Hz), 3.15 (dd, 1H, H-5, *J* 3.5 Hz, *J* 2.0 Hz), 3.36 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.0 Hz), 3.66 (ddd, 1H, H-6', *J* 14.0 Hz, *J* 9.0 Hz, *J* 7.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-9), 15.5 (C-11 or C-12), 18.5 (C-11 or C-12), 20.1 (C-8), 28.1 (C-10), 29.1 (C-7), 40.0 (C-6), 41.7 (C-3), 44.9 (C-4), 72.6 (C-5), 173.0 (C-2). ***m/z*** (ES+) 199 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{22}N_2ONa^+$) requires ***m/z*** 221.1624, found ***m/z*** 221.1623.

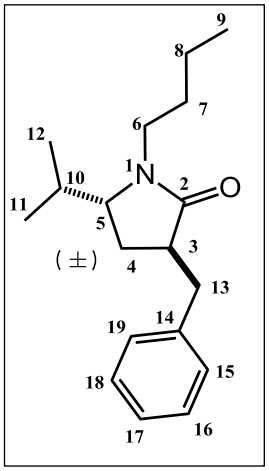
A.3.10. 3-Benzyl-1-butyl-5-isopropylpyrrolidin-2-one 209

A 10 mL, flame-dried, one-necked flask, purged with nitrogen, was charged with major 3-benzyl-1-butyl-5-isopropyl-4-nitropyrrolidin-2-one **193aaa** (50 mg, 0.16 mmol, 1 eq) and freshly distilled toluene. The mixture was degassed and purged three times with vacuum and nitrogen. Then, azo-bis-isobutyronitrile (AIBN) (5.3 mg, 0.032 mmol, 0.2 eq) was added, along with tributylstannane (233 mg, 0.80 mmol, 6.0 eq). The mixture was pumped/filled three times with nitrogen again. The flask was put in an oil bath previously heated to 150 ˚C and stirred overnight. A TLC (petroleum ether / diethyl

ether 1:1) showed full conversion of starting material. The purification was achieved by flash column chromatography (pure petroleum ether, then gradient from petroleum ether / diethyl ether 3:1 to 1:1).



IR (cm^{-1}) ν_{max} 1687 (C=O). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.61 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.85 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 0.93 (t, 3H, H-9, *J* 7.5 Hz), 1.24-1.38 (m, 3H, H-8 and H-4), 1.39-1.53 (m, 2H, H-7), 1.85 (ddd, 1H, H-4', *J* 13.0 Hz, *J* 9.0 Hz, *J* 7.5 Hz), 2.08 (dsept, 1H, H-10, *J* 7.0 Hz, *J* 4.0 Hz), 2.59-2.70 (m, 2H, H-3 and H-13), 2.76 (ddd, 1H, H-6, *J* 13.5 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.29 (dd, 1H, H-13', *J* 13.5 Hz, *J* 3.5 Hz), 3.47 (ddd, 1H, H-5, *J* 8.5 Hz, *J* 7.5 Hz, *J* 4.0 Hz), 3.77 (ddd, 1H, H-6', *J* 13.5 Hz, *J* 9.0 Hz, *J* 8.0 Hz), 7.17-7.24 (m, 3H, H-15, H-17 and H-19), 7.25-7.32 (m, 2H, H-16 and H-18). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.7 (C-11 or C-12), 13.8 (C-12 or C-11), 18.3 (C-9), 20.2 (C-8), 23.6 (C-4), 26.7 (C-10), 28.9 (C-7), 37.0 (C-13), 39.7 (C-6), 42.9 (C-3), 59.3 (C-5), 126.1 (C-17), 128.4 (C-16 and C-18), 129.0 (C-15 and C-19), 139.8 (C-14), 176.3 (C-2). ***m/z*** (ES+) 296 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{27}NONa^+$) requires ***m/z*** 296.1985, found ***m/z*** 296.1985.



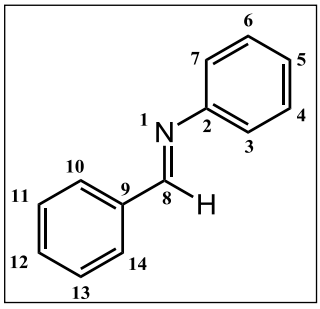
A 10 mL, flame-dried, one-necked flask, purged with nitrogen, was charged with minor 3-benzyl-1-butyl-5-isopropyl-4-nitropyrrolidin-2-one 193 **aaa**(50 mg, 0.16 mmol, 1.0 eq) and freshly distilled toluene. The mixture was degassed and purged three times with vacuum and nitrogen. Then, azo-bis-isobutyronitrile (AIBN) (5.3 mg, 0.032 mmol, 0.2 eq) was added, along with tributylstannane (233 mg, 0.80 mmol, 6.0 eq). The mixture was again degassed and purged three times with vacuum and nitrogen. The flask was put in an oil bath previously heated to 150 ˚C and stirred overnight. A TLC (petroleum ether / diethyl ether 1:1) showed full conversion of starting material. The purification was achieved by flash column chromatography (pure petroleum ether, then gradient from petroleum ether / diethyl ether 3:1 to 1:1).

IR (cm^{-1}) ν_{max} 1683 (C=O). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 0.71 (d, 3H, H-11 or H-12, *J* 7.0 Hz), 0.86 (d, 3H, H-12 or H-11, *J* 7.0 Hz), 0.92 (t, 3H, H-9, *J* 7.5 Hz), 1.23-1.33 (m, 2H, H-8), 1.33-1.44 (m, 1H, H-7), 1.44-1.54 (m, 1H, H-7'), 1.61-1.70 (m, 1H, H-4), 1.80 (ddd, 1H, H-4', *J* 13.5 Hz, *J* 9.5 Hz, *J* 3.5 Hz), 2.02 (septd, 1H, H-10, *J* 7.0 Hz, *J* 3.5 Hz), 2.63 (dd, 1H, H-13, *J* 13.5 Hz, *J* 9.5 Hz), 2.70-2.78 (m, 1H, H-3), 2.81 (ddd, 1H, H-6, *J* 13.5 Hz, *J* 8.5 Hz, *J* 5.0 Hz), 3.21 (dd, 1H, H-13', *J* 13.5 Hz, *J* 4.0 Hz), 3.38 (dt, 1H, H-5, *J* 9.0 Hz, *J* 3.5 Hz), 3.70 (ddd, 1H, H-6', *J* 13.5 Hz, *J* 9.0 Hz, *J* 7.5 Hz), 7.18-7.24 (m, 3H, H-15, H-17 and H-19), 7.26-7.32 (m, 2H, H-16 and H-18). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 13.8 (C-9), 14.5 (C-11 or C-12), 18.7 (C-12 or C-11), 20.1 (C-8), 24.0 (C-4), 28.2 (C-10), 29.0 (C-7), 37.9 (C-13), 40.0 (C-6), 43.1 (C-3), 60.1 (C-5), 126.2 (C-17), 128.4 (C16 and C-18), 129.1 (C-15 and C-19), 139.5 (C-14), 175.9 (C-2). ***m/z*** (ES+) 296 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{27}NONa^+$) requires ***m/z*** 296.1985, found ***m/z*** 296.1980.

A.4 Experimental- Chapter 4

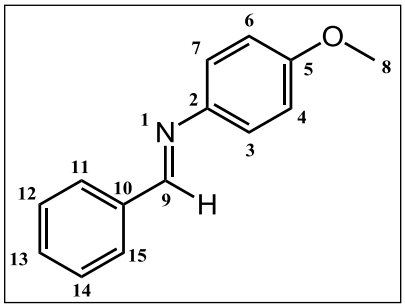
All the preformed acyclic imines were obtained by mixing the corresponding aldehyde (1 eq) and the corresponding amines (1eq) in dichloromethane with sodium sulfate. The reactions were allowed to stir at romm temperature overnight, then the imines were quickly purified by flash column chromatography (dichloromethane / ethyl acetate 10:1).

A.4.1. *N*,1-diphenylmethanimine



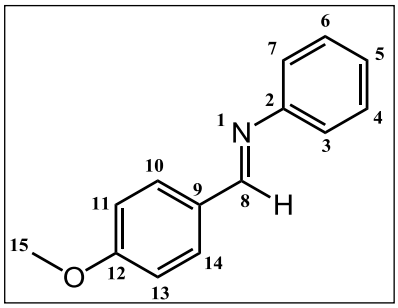
mp 46-47 ˚C. **IR** (cm^{-1}) ν_{max} 1626 (C=N), 1590 (C=C), 1578 (C=C), 1484 (C=C), 1451 (C=C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.22-7.32 (m, 3H, H_{Ar}), 7.38-7.47 (m, 2H, H_{Ar}), 7.47-7.56 (m, 3H, H_{Ar}), 7.89-7.98 (m, 2H, H_{Ar}), 8.49 (s, 1H, H-8). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 120.9 (2x C_{Ar}-H), 125.9 (C_{Ar}-H), 128.8 (2x C_{Ar}-H), 128.9 (2x C_{Ar}-H), 129.2 (2x C_{Ar}-H), 131.4 (2x C_{Ar}-H), 136.2 (C_{quat}), 152.1 (C_{quat}), 160.4 (C-8). ***m/z*** (ES+) 182 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}N^+$) requires ***m/z*** 182.0964, found ***m/z*** 182.0965.

A.4.2. *N*-(4-methoxyphenyl)-1-phenylmethanimine



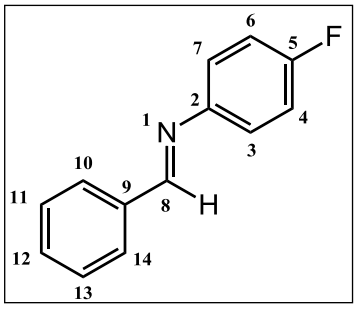
mp 64-66 ˚C. **IR** (cm^{-1}) ν_{max} 1623 (C=N), 1601 (C=C), 1577 (C=C), 1505 (C=C), 1466 (C=C), 1247 (C-O-C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.85 (s, 3H, H-8), 6.88-7.06 (m, 2H, H_{Ar}), 7.20-7.36 (m, 2H, H_{Ar}), 7.42-7.56 (m, 3H, H_{Ar}), 7.89-7.93 (m, 2H, H_{Ar}), 8.50 (s, 1H, H-9). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.5 (C-8), 114.4 (2x C_{Ar}-H), 122.2 (2x C_{Ar}-H), 128.6 (2x C_{Ar}-H), 128.7 (2x C_{Ar}-H), 131.0 (C-13), 136.4 (C_{quat}), 144.9 (C_{quat}), 158.3 (C_{quat}), 158.4 (C-9). ***m/z*** (ES+) 212 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{14}NO^+$) requires ***m/z*** 212.1070, found ***m/z*** 212.1077.

A.4.3. 1-(4-methoxyphenyl)-*N*-phenylmethanimine



mp 61-63 ˚C. **IR** (cm^{-1}) ν_{max} 1624 (C=N), 1605 (C=C), 1587 (C=C), 1510 (C=C), 1463 (C=C), 1250 (C-O-C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.89 (s, 3H, H-15), 6.96-7.07 (m, 2H, H_{Ar}), 7.17-7.25 (m, 3H, H_{Ar}), 7.36-7.45 (m, 2H, H_{Ar}), 7.81-7.93 (m, 2H, H_{Ar}), 8.40 (s, 1H, H-8). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.4 (C-15), 114.2 (2x C_{Ar}-H), 120.9 (2x C_{Ar}-H), 125.5 (C-5), 129.1 (2x C_{Ar}-H), 129.3 (C_{quat}), 130.5 (2x C_{Ar}-H), 152.4 (C_{quat}), 159.7 (C_{quat}), 162.2 (C-8). ***m/z*** (ES+) 212 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{14}NO^+$) requires ***m/z*** 212.1070, found ***m/z*** 212.1066.

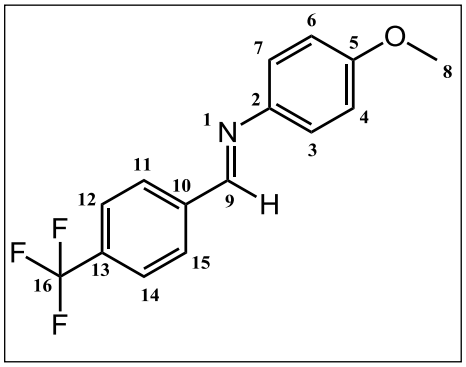
A.4.4. *N*-(4-fluorophenyl)-1-phenylmethanimine



IR (cm^{-1}) ν_{max} 1628 (C=N), 1601 (C=C), 1578 (C=C), 1501 (C=C), 1451 (C=C), 1092 (C-F). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.01-7.15 (m, 2H, H_{Ar}), 7.16-7.25 (m, 2H, H_{Ar}), 7.42-7.56 (m, 3H, H_{Ar}), 7.84-7.97 (m, 2H, H_{Ar}), 8.46 (s, 1H, H-8). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 115.8 (C_{Ar}-H), 116.0 (C_{Ar}-H), 122.2 (C_{Ar}-H), 122.3 (C_{Ar}-H), 128.7 (2x C_{Ar}-H), 128.8 (2x C_{Ar}-H), 131.4 (C_{Ar}-H), 136.1 (C_{quat}), 160.1 (C_{quat}), 160.2 (C_{quat}), 162.5 (C-8). ***m/z*** (ES+) 200 ($[M+H]^+$, 100%),

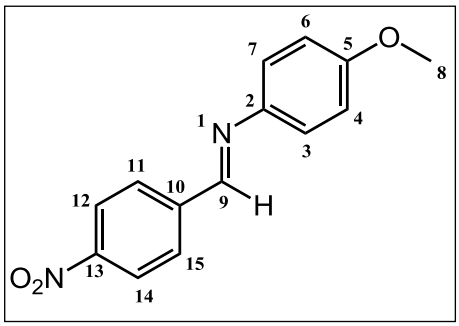
HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{11}FN^+$) requires ***m/z*** 200.0870, found ***m/z*** 200.0876.

A.4.5. *N*-(4-methoxyphenyl)-1-[4-(trifluoromethyl)phenyl]methanimine



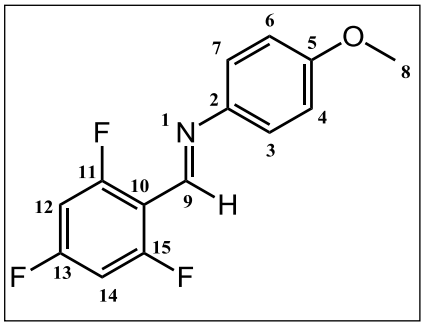
mp 130-132 ˚C. **IR** (cm^{-1}) ν_{max} 1623 (C=N), 1595 (C=C), 1575 (C=C), 1504 (C=C), 1462 (C=C), 1254 (C-O-C), 1124 (C-F), 1104 (C-F). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.85 (s, 3H, H-8), 6.86-7.09 (m, 2H, H_{Ar}), 7.19-7.38 (m, 2H, H_{Ar}), 7.72 (d, 2H, H_{Ar}, *J* 8.0 Hz), 8.01 (d, 2H, H_{Ar}, *J* 8.0 Hz), 8.54 (s, 1H, H-9). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.5 (C-8), 114.5 (2x C_{Ar}-H), 122.4 (2x C_{Ar}-H), 125.3 (C_{Ar}-H), 125.7 (q, C-16, *J* 4.0 Hz), 128.7 (2x C_{Ar}-H), 132.2 (C_{Ar}-H), 132.5 (C_{Ar}-H), 139.6 (C_{quat}), 144.1 (C_{quat}), 158.2 (C_{quat}), 158.8 (C-9). ***m/z*** (ES+) 280 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{13}FNO_3^+$) requires ***m/z*** 280.0944, found ***m/z*** 280.0943.

A.4.6. *N*-(4-methoxyphenyl)-1-(4-nitrophenyl)methanimine



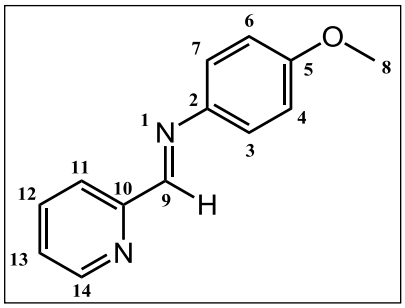
mp 132-133 ˚C. **IR** (cm^{-1}) ν_{max} 1624 (C=N), 1600 (C=C), 1577 (C=C), 1515 (NO_2), 1509 (C=C), 1463 (C=C), 1515 (NO_2), 1246 (C-O-C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.86 (s, 3H, H-8), 6.92-7.11 (m, 2H, H_{Ar}), 7.29-7.46 (m, 2H, H_{Ar}), 7.98-8.15 (m, 2H, H_{Ar}), 8.26-8.46 (m, 2H, H_{Ar}), 8.59 (s, 1H, H-9). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.5 (C-9), 114.5 (2x C_{Ar}-H), 122.6 (2x C_{Ar}-H), 124.0 (2x C_{Ar}-H), 129.1 (2x C_{Ar}-H), 141.9 (C_{quat}), 143.6 (C_{quat}), 149.0 (C_{quat}), 154.8 (C_{quat}), 159.2 (C-9). ***m/z*** (ES+) 279 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{12}N_2O_3Na^+$) requires ***m/z*** 279.0740, found ***m/z*** 279.0744.

A.4.7. *N*-(4-methoxyphenyl)-1-(2,4,6-trifluorophenyl)methanimine 227



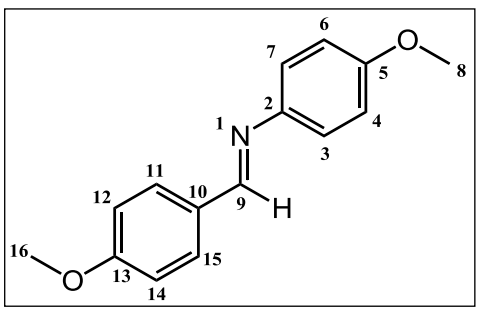
mp 89-92 ˚C. **IR** (cm^{-1}) ν_{max} 1619 (C=N), 1600 (C=C), 1578 (C=C), 1504 (C=C), 1468 (C=C), 1247 (C-O-C), 1042 (C-F), 1029 (C-F), 1002 (C-F). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.85 (s, 3H, H-8), 6.67-6.86 (m, 2H, H_{Ar}), 6.88-7.11 (m, 2H, H_{Ar}), 7.15-7.39 (m, 2H, H_{Ar}), 8.60 (s, 1H, H-9). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.5 (C-9), 100.8 (C_{Ar}-H), 101.1 (C_{Ar}-H), 101.3 (C_{Ar}-H), 114.4 (2x C_{Ar}-H), 122.2 (2x C_{Ar}-H), 145.1 (C_{quat}), 148.1 (C_{quat}), 158.8 (C-9), 161.1 (C_{Ar}-F), 162.3 (C_{Ar}-F), 163.8 (C_{Ar}-F). ***m/z*** (ES+) 288 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{14}H_{10}F_3NONa^+$) requires ***m/z*** 288.0607, found ***m/z*** 288.0607.

A.4.8. *N*-(4-methoxyphenyl)-1-(pyridin-2-yl)methanimine



IR (cm^{-1}) ν_{max} 1625 (C=N), 1598 (C=C), 1578 (C=C), 1504 (C=C), 1466 (C=C), 1244 (C-O-C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.84 (s, 3H, H-8), 6.89-7.01 (m, 2H, H_{Ar}), 7.29-7.41 (m, 3H, H_{Ar}), 7.80 (td, 1H, H_{Ar}, *J* 8.0 Hz, *J* 1.5 Hz), 8.19 (d, 1H, H_{Ar}, *J* 8.0 Hz), 8.63 (s, 1H, H-9), 8.67-8.77 (m, 1H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.5 (C-8), 114.4 (2x C_{Ar}-H), 121.6 (C_{Ar}-H), 122.7 (2x C_{Ar}-H), 124.8 (C_{Ar}-H), 136.6 (C_{Ar}-H), 143.7 (C_{quat}), 149.6 (C_{Ar}-H), 154.9 (C_{quat}), 158.2 (C-9), 158.93 (C_{quat}). ***m/z*** (ES+) 235 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{13}H_{12}N_2O^+$) requires ***m/z*** 235.0842, found ***m/z*** 235.0842.

A.4.9. *N*,1-bis(4-methoxyphenyl)methanimine



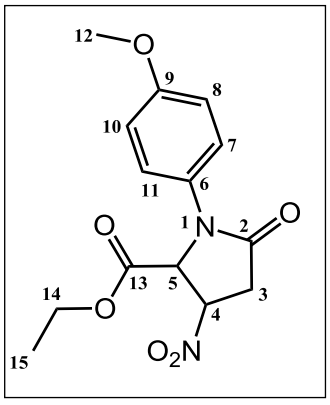
mp 143-145 ˚C. **IR** (cm^{-1}) ν_{max} 1622 (C=N), 1607 (C=C), 1577 (C=C), 1511 (C=C), 1469 (C=C), 1251 (C-O-C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.84 (s, 3H, H-8 or H-16), 3.88 (s, 3H, H-16 or H-8), 6.91-6.96 (m, 2H, H_{Ar}), 6.96-7.02 (m, 2H, H_{Ar}), 7.19-7.25 (m, 2H, H_{Ar}), 7.81-7.89 (m, 2H, H_{Ar}), 8.42 (s, 1H, H-9). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 55.4 (C-8 or C-16), 55.5 (C-16 or C-8), 114.1 (2x C_{Ar}-H), 114.3 (2x C_{Ar}-

H), 122.1 (2x C_{Ar}-H), 114.3 (C_{quat}), 130.2 (2x C_{Ar}-H), 145.3 (C_{quat}), 157.9 (C_{quat}), 158.0 (C_{quat}), 162.0 (C-9). ***m/z*** (ES+) 242 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}NO_2^+$) requires ***m/z*** 242.1176, found ***m/z*** 242.1175.

A.4.10. General procedure F for the synthesis of pyrrolidin-2-one 226

A 5 mL one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with methyl-3-nitropropanoate **169** (50 mg, 0.38 mmol, 1.0 eq), chiral phophoric acid **180** (0.04 mmol, 0.1 eq), the corresponding preformed imine (1.5 eq) and toluene (0.05M). The reaction mixture was pumped/filled three times with N_2 and it was allowed to stir at 70 °C, under a N_2 atmosphere, for 48 hours. The crude mixture was concentrated under vacuum, the residue was taken up in dichloromethane and purified by flash column chromatography.

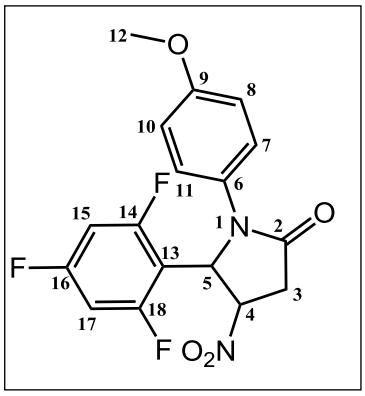
A.4.10.1. Ethyl 1-(4-methoxyphenyl)-3-nitro-5-oxoprolinate 226a



226a was obtained in 45% yield (single diastereisomer, 85% ee) as a dark yellow oil.

IR (cm^{-1}) ν_{max} 1743 (C=O), 1716 (C=O), 1610 (C=C), 1561 (NO_2), 1513 (C=C), 1367 (NO_2), 1250 (C-O-C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.25 (t, 3H, H-15, *J* 7.0 Hz), 3.22-3.26 (m, 2H, H-3), 3.81 (s, 3H, H-12), 4.25 (q, 2H, H-14, *J* 7.0 Hz), 5.17 (ddd, 1H, H-4, *J* 6.0 Hz, *J* 4.0 Hz, *J* 1.5 Hz), 5.22 (d, 1H, H-5, *J* 1.5 Hz), 6.93 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 7.31 (d, 2H, H-7 and H-11, *J* 9.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.0 (C-15), 35.6 (C-3), 55.5 (C-12), 63.0 (C-14), 66.1 (C-5), 79.8 (C-4), 114.6 (C-8 and C-10), 125.8 (C-7 and C-11), 129.0 (C-6), 158.6 (C-9), 167.9 (C-2), 169.1 (C-13). ***m/z*** (ES+) 331 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}F_3N_2O_6Na^+$) requires ***m/z*** 331.0901, found ***m/z*** 331.0902.

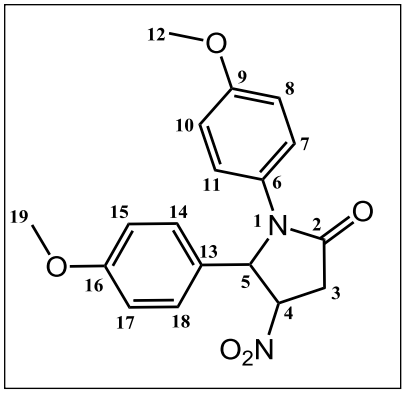
A.4.10.2. 1-(4-Methoxyphenyl)-4-nitro-5-(2,4,6-trifluorophenyl)pyrrolidin-2-one 226b



226b was obtained in 40% yield (single diastereisomer, 83% ee) as a dark yellow oil.

IR (cm^{-1}) ν_{max} 1711 (C=O), 1638 (C=C), 1607 (C=C), 1560 (NO_2), 1513 (C=C), 1367 (NO_2), 1251 (C-O-C), 1035 (C-F). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.31-3.52 (m, 2H, H-3), 3.76 (s, 3H, H-12), 5.26 (ddd, 1H, H-4, *J* 9.0 Hz, *J* 5.0 Hz, *J* 3.5 Hz), 6.01 (d, 1H, H-5, *J* 3.5 Hz), 6.64-6.71 (m, 2H, H-15 and H-17), 6.34 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 7.17 (d, 2H, H-7 and H-11, *J* 9.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 36.4 (C-3), 55.8 (C-12), 58.4 (C-5), 82.7 (C-4), 101.6 (C-15 or C-17), 101.8 (C-17 or C-15), 115.0 (C-8 an C-10), 126.2 (C-7 and C-11), 128.6 (C_{quat}), 158.9 (C-9), 160.7 (C-F), 160.9 (C-F), 162.8 (C-F), 168.9 (C-2). ***m/z*** (ES+) 389 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{13}F_3N_2O_4Na^+$) requires ***m/z*** 389.0720, found ***m/z*** 389.0720.

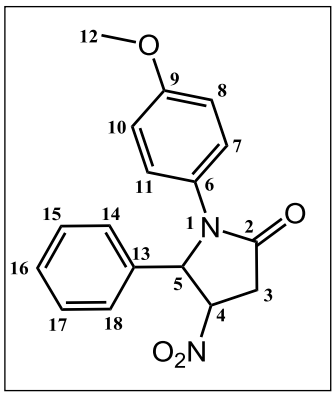
A.4.10.3. 1,5-Bis(4-methoxyphenyl)-4-nitropyrrolidin-2-one 226g



226g was obtained in 15% yield (single diastereisomer, 0% ee) as a dark yellow oil.

IR (cm^{-1}) ν_{max} 1704 (C=O), 1612 (C=C), 1556 (NO_2), 1513 (C=C), 1367 (NO_2), 1251 (C-O-C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.17-3.36 (m, 2H, H-3), 3.75 (s, 3H, H-12), 3.80 (s, 3H, H-19), 4.90-4.99 (m, 1H, H-4), 5.59 (d, 1H, H-5, *J* 2.0 Hz), 6.81 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 6.91 (d, 2H, H_{Ar}, *J* 9.0 Hz), 7.20 (d, 2H, H_{Ar}, *J* 8.5 Hz), 7.28 (d, 2H, H_{Ar}, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 35.0 (C-3), 55.4 (C-12 and C-19), 68.0 (C-5), 85.0 (C-4), 114.3 (2x C_{Ar}-H), 115.0 (2x C_{Ar}-H), 124.4 (2x C_{Ar}-H), 127.3 (2x C_{Ar}-H), 128.4 (C-6 or C-13), 129.8 (C-13 or C-6), 157.6 (C-9 or C-16), 160.2 (C-16 or C-9), 169.2 (C-2). ***m/z*** (ES+) 365 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{18}N_2O_5Na^+$) requires ***m/z*** 365.1108, found ***m/z*** 365.1116.

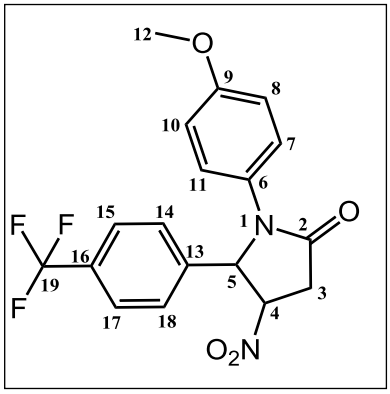
A.4.10.4. 1-(4-Methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one 226h



226h was obtained in 54% yield (single diastereisomer, 56% ee) as a brown oil.

IR (cm^{-1}) ν_{max} 1706 (C=O), 1610 (C=C), 1556 (NO_2), 1513 (C=C), 1368 (NO_2), 1251 (C-O-C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.17-3.38 (m, 2H, H-3), 3.75 (s, 3H, H-12), 4.97 (dt, 1H, H-4, *J* 7.5 Hz, *J* 2.0 Hz), 5.66 (d, 1H, H-5, *J* 2.0 Hz), 6.82 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 7.23-7.37 (m, 4H, H_{Ar}), 7.37-7.58 (m, 3H, H_{Ar}). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 35.0 (C-3), 55.4 (C-12), 68.3 (C-5), 84.8 (C-4), 114.3 (C-8 an C-10), 124.3 (2x C_{Ar}-H), 126.0 (2x C_{Ar}-H), 129.3 (C-16), 129.7 (2x C_{Ar}-H), 136.6 (C-13), 157.6 (C-9), 169.3 (C-2). ***m/z*** (ES+) 335 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{16}N_2O_4Na^+$) requires ***m/z*** 335.1002, found ***m/z*** 335.1006.

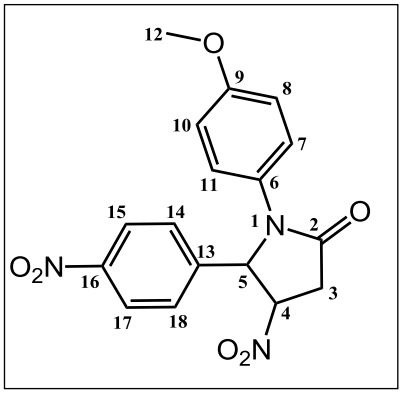
A.4.10.5 1-(4-Methoxyphenyl)-4-nitro-5-[4-(trifluoromethyl)phenyl]pyrrolidin-2-one 226i



226i was obtained in 38% yield (single diastereisomer, 79% ee) as a brown oil.

IR (cm^{-1}) ν_{max} 1707 (C=O), 1620 (C=C), 1557 (NO_2), 1512 (C=C), 1366 (NO_2), 1251 (C-O-C), 1125 (C-F), 1120 (C-F). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.17-3.42 (m, 2H, H-3), 3.76 (s, 3H, H-12), 4.94 (dt, 1H, H-4, *J* 8.0 Hz, *J* 2.0 Hz), 5.76 (d, 1H, H-5, *J* 2.0 Hz), 6.84 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 7.29 (d, 2H, H-7 and H-11, *J* 9.0 Hz), 7.45 (d, 2H, H_{Ar}, *J* 8.0 Hz), 7.68 (d, 2H, H_{Ar}, *J* 9.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 34.8 (C-3), 55.4 (C-12), 67.6 (C-5), 84.3 (C-4), 114.5 (C-8 and C-10), 124.2 (C-7 and C-11), 126.6 (C-14, C-15, C-17 and C-18), 126.7 (q, C-19, *J* 4.0 Hz), 129.3 (C_{quat}), 131.5 (C_{quat}), 140.7 (C-13), 157.8 (C-9), 169.0 (C-2). ***m/z*** (ES+) 403 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{16}F_3N_2O_4Na^+$) requires ***m/z*** 403.0876, found ***m/z*** 403.0876.

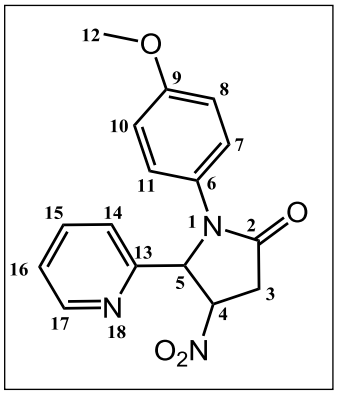
A.4.10.6. 1-(4-Methoxyphenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidin-2-one 226j



226j was obtained in 40% yield (single diastereisomer, 82% ee) as a brown oil.

IR (cm^{-1}) ν_{max} 1706 (C=O), 1612 (C=C), 1556 (NO_2), 1514 (C=C), 1367 (NO_2), 1250 (C-O-C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.24 (dd, 1H, H-3, *J* 18.0 Hz, *J* 8.5 Hz), 3.40 (dd, 1H, H-3', *J* 18.0 Hz, *J* 3.0 Hz),3.75 (s, 3H, H-12), 4.96 (dt, 1H, H-4, *J* 8.5 Hz, *J* 3.0 Hz), 5.81 (d, 1H, H-5, *J* 3.0 Hz), 6.83 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 7.27 (d, 2H, H-7 and H-11, *J* 9.0 Hz), 7.51 (d, 2H, H-14 and H-18, *J* 8.5 Hz), 8.27 (d, 2H, H-15 and H-17, *J* 8.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 34.8 (C-3), 55.4 (C-12), 67.2 (C-5), 84.0 (C-4), 114.5 (C-8 and C-10), 124.3 (C-7 and C-11), 124.9 (C-15 and C-17), 127.3 (C-14 and C-18), 128.9 (C-6), 143.7 (C-13), 148.4 (C-16), 158.0 (C-9), 168.7 (C-2). ***m/z*** (ES+) 380 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{15}F_3N_3O_6Na^+$) requires ***m/z*** 380.0853, found ***m/z*** 380.0859.

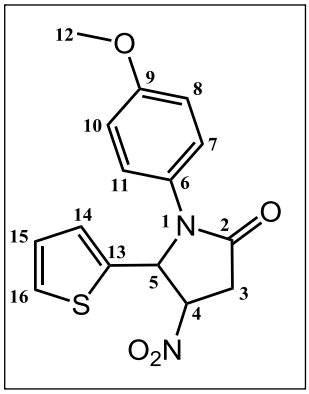
A.4.10.7. 1-(4-Methoxyphenyl)-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one 226k



226k was obtained in 45% yield (single diastereisomer, 56% ee) as a brown oil.

IR (cm^{-1}) ν_{max} 1705 (C=O), 1609 (C=C), 1556 (NO_2), 1513 (C=C), 1367 (NO_2), 1250 (C-O-C). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.31 (dd, 1H, H-3, *J* 18.0 Hz, *J* 2.0 Hz), 3.45 (dd, 1H, H-3', *J* 18.0 Hz, *J* 8.5 Hz),3.76 (s, 3H, H-12), 5.28-5.37 (m, 1H, H-4), 5.66 (d, 1H, H-5, *J* 1.5 Hz), 6.82 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 7.12-7.21 (m, 3H, H-7, H-11 and H_{Ar}), 7.26-7.31 (m, 1H, H_{Ar}), 7.65 (td, 1H, H_{Ar}, *J* 7.5 Hz, *J* 1.5 Hz), 8.66 (d, 1H, H_{Ar}, *J* 4.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 35.9 (C-3), 55.4 (C-12), 69.1 (C-5), 82.8 (C-4), 114.4 (C-8 and C-10), 122.3 (C-14 or C-16), 124.0 (C-16 or C-14), 125.7 (C-7 and C-11), 129.4 (C-6), 137.2 (C-15), 150.7 (C-17), 155.5 (C-13), 158.1 (C-9), 169.8 (C-2). ***m/z*** (ES+) 314 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{15}N_3O_4Na^+$) requires ***m/z*** 336.0955, found ***m/z*** 336.0954.

A.4.10.8. 1-(4-Methoxyphenyl)-4-nitro-5-(2-thienyl)pyrrolidin-2-one 226l

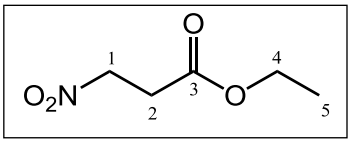


226l was obtained in 50% yield (single diastereisomer, 53% ee) as a brown oil.

IR (cm^{-1}) ν_{max} 1707 (C=O), 1610 (C=C), 1556 (NO_2), 1512 (C=C), 1362 (NO_2), 1251 (C-O-C). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.28 (dd, 1H, H-3, *J* 18.5 Hz, *J* 3.0 Hz), 3.37 (dd, 1H, H-3', *J* 18.5 Hz, *J* 7.5 Hz), 3.77 (s, 3H, H-12), 5.09 (ddd, 1H, H-4, *J* 7.5 Hz, *J* 3.0 Hz, *J* 2.0 Hz), 5.91 (d, 1H, H-5, *J* 2.0 Hz), 6.85 (d, 2H, H-8 and H-10, *J* 9.0 Hz), 6.98 (dd, 1H, H_{Ar}, *J* 5.0 Hz, *J* 3.5 Hz), 7.04 (br d, 1H, H_{Ar}, *J* 3.5 Hz), 7.27 (d, 2H, H-7 and H-11, *J* 9.0 Hz), 7.33 (dd, 1H, H_{Ar}, *J* 5.0 Hz, *J* 1.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 35.1 (C-3), 55.4 (C-12), 64.4 (C-5), 84.7 (C-4), 114.4 (C-8 and C-10), 125.4 (C-7 and C-11), 126.7 (2x C_{Ar}-H), 126.8 (C_{Ar}-H), 127.6 (C_{Ar}-H), 129.1 (C-6), 139.9 (C-13), 158.2 (C-9), 168.6 (C-2). ***m/z*** (ES+) 341 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{14}N_2O_4SNa^+$) requires ***m/z*** 341.0566, found ***m/z*** 341.0563.

A.5 Experimental- Chapter 5

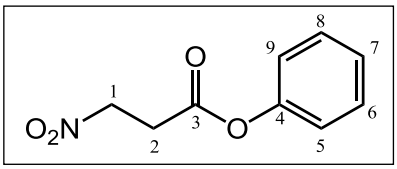
A.5.1. Ethyl 3-nitropropanoate 240



A 50 mL, one-necked flask equipped with a magnetic stirrer and an additional funnel containing 3Å molecular sieves, was charged with 3-nitropropanoic acid (1.0 g, 84.0 mmol, 1.0 eq), ethanol (20 mL) and sulphuric acid (0.2 mL). The mixture was refluxed for 4 hours. Ethanol was evaporated to give a brown residue which was taken up in dichloromethane and washed three times with water. The combined aqueous layers were extracted once with dichloromethane. The combined organic layers were dried over Na_2SO_4 and dichloromethane was removed under vacuum to give a yellow oil which was purified by flash column chromatography (petroleum ether / diethyl ether 2:1) to give 0.6 g (54 % yield) of **240** as a light yellow oil.

IR (cm^{-1}) ν_{max} 1732 (C=O), 1556 (NO_2), 1378 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.28 (t, 3H, H-5, *J* 7.0 Hz), 2.97 (t, 2H, H-2, *J* 6.0 Hz), 4.20 (q, 2H, H-4, *J* 7.0 Hz), 4.66 (t, 2H, H-1, *J* 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.0 (C-5), 31.1 (C-2), 61.5 (C-4), 69.7 (C-1), 169.4 (C-3). ***m/z*** HRMS (TOF MS FI+) exact mass calculated for $[M]^+$ ($C_5H_9NO_4^+$) requires ***m/z*** 147.0532, found ***m/z*** 147.0532.

A.5.2. Phenyl 3-nitropropanoate 241



A 25 mL, one-necked flask, equipped with magnetic stirring and a nitrogen balloon, was charged with phenol (0.8 g, 8.4 mmol, 1.0 eq), 3-nitropropanoic acid (1.0 g, 8.4 mmol, 1.0 eq) and ethyl acetate (10 mL). To this, with stirring, was added *N*,*N*-diisopropylcarbodiimide (1.3 mL, 8.4 mmol, 1.0 eq) dropwise. The mixture was stirred at room temperature overnight. The reaction mixture was then filtered over celite and reduced under vacuum. The purification was achieved by flash column chromatography (petroleum ether/diethyl ether 4:1, R_f = 0.38) to give 0.9 g (56% yield) of **241** as a brown oil.

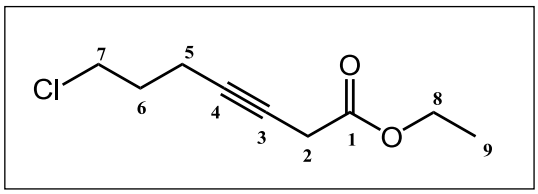
IR (cm^{-1}) ν_{max} 1761 (C=O), 1592 (C=C aromatic), 1557 (NO_2), 1493 (C=C aromatic), 1381 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 3.24 (t, 2H, H-2, *J* 6.0 Hz), 4.77 (t, 2H, H-1, *J* 6.0 Hz), 7.09-7.13 (m, 2H, H-5 and H-9), 7.21-7.31 (m, 1H, H-7), 7.36-7.47 (m, 2H, H-6 and H-8). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 31.2 (C-2), 69.6 (C-1), 121.3 (C-5 and C-9), 126.3 (C-7), 129.6 (C-6 and C-8), 150.2 (C-4), 168.1 (C-3). ***m/z*** HRMS (TOF MS FI+) exact mass calculated for $[M]^+$ ($C_9H_9NO_4^+$) requires ***m/z*** 195.0532, found ***m/z*** 195.0531.

A.6 Experimental- Chapter 6

A.6.1. Ethyl 7-cholorohept-3-yonate 294

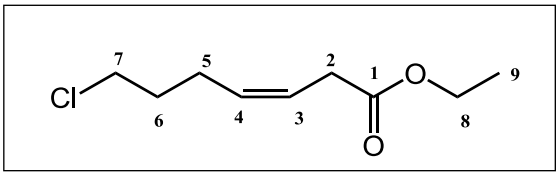
In a one-necked flask equipped with a magnetic stirrer bar, a suspension of 5-chloro-1-pentyne (3.00 g, 29.3 mmol, 1.00 eq) and copper iodide (0.28 g, 1.4 mmol, 0.05 eq) in acetonitrile was stirred under pour ton SIa nitrogen atmosphere. Ethyldiazoacetate (5.00 g, 43.9 mmol, 1.50 eq) was added and the reaction was allowed to stir at room temperature overnight. The reaction was followed by TLC

(petroleum ether / diethyl ether 10:1). The mixture was concentrated under vacuum and the crude residue was purified by flash column chromatography (petroleum ether / diethyl ether 20:1) to give 5.00 g (90 % yield, 97% purity by ^{1}H NMR) of ethyl 7-chlorohep-3-yonate **294** as a yellow oil.



IR (cm^{-1}) ν_{max} 1730 (C=O). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.28 (t, 3H, H-9, *J* 7.5 Hz), 1.96 (quint, 2H, H-6, *J* 6.5 Hz), 2.39 (tt, 2H, H-5, *J* 6.5 Hz, *J* 2.5 Hz), 3.24 (t, 2H, H-2, *J* 2.5 Hz), 3.66 (t, 2H, H-7, *J* 6.5 Hz), 4.18 (q, 2H, H-8, *J* 7.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.1 (C-9), 16.2 (C-5), 26.0 (C-2), 31.3 (C-6), 43.6 (C-7), 61.5 (C-8), 72.7 (C-3), 81.7 (C-4), 168.7 (C-1). ***m/z*** (ES+) 189 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_9H_{13}ClO_2Na^+$) requires ***m/z*** 211.0496, found ***m/z*** 211.0501.

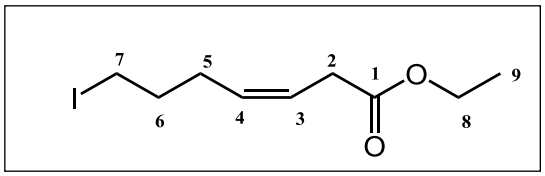
A.6.2. (*Z*)-Ethyl 7-cholorohept-3-enoate 293



In a one-necked flask equipped with a magnetic stirrer bar and a balloon of hydrogen, nickel (II) chloride (3.8 g, 15.9 mmol, 1 eq) was dissolved in ethanol (80 mL). In a separate one-necked flask, sodium borohydride (1.2 g, 31.8 mmol, 2 eq) was dissolved in ethanol (0.5 M). The sodium borohydride solution was added dropwise to the nickel (II) chloride solution, followed by addition of ethylene diamine (1.7 mL, 31.8 mmol, 2 eq). The mixture was purged three times with H_2, and stirred under an atmosphere of H_2 for 30 minutes. Ethyl chlorohep-3-yonate **294** (3.0 g, 15.9 mmol, 1 eq) was then added to the reaction mixture in one portion. The mixture was purged three times with H_2, then stirred under an atmosphere of H_2 for 2 hours. The ethanol was removed under vacuum, providing a black solid residue which was redissolved in ethyl acetate and water / ammonia solution (1:1). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The purification was achieved by flash column chromatography (petroleum ether / ethyl acetate 10:1) to give 2.4 g ethyl (3Z)-7-chlorohept-3-enoate **293** (77% yield, *Z* / *E* > 99:1) as a colourless oil.

IR (cm^{-1}) ν_{max} 1741 (C=O). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.26 (t, 3H, H-9, *J* 7.0 Hz), 1.85 (quint, 2H, H-6, *J* 7.0 Hz), 2.23 (br q, 2H, H-5, *J* 7.0 Hz), 3.11 (br d, 2H, H-2, *J* 7.5 Hz), 3.54 (t, 2H, H-7, *J* 7.0 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 5.50-5.57 (m, 1H, H-4), 5.61-5.68 (m, 1H, H3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.2 (C-9), 24.4 (C-5), 31.9 (C-6), 32.9 (C-2), 44.3 (C-7), 60.6 (C-8), 122.7 (C-3), 131.1 (C-4), 171.8 (C-1). ***m/z*** (ES+) 191 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{16}ClO_2^+$) requires ***m/z*** 191.0833, found ***m/z*** 191.0838.

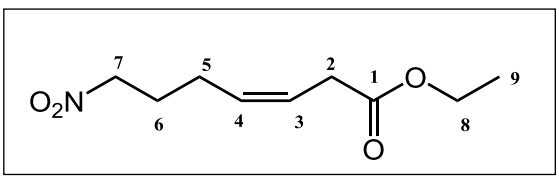
A.6.3. (*Z*)-Ethyl 7-iodohept-3-enoate 292



In a one-necked flask, equipped with a magnetic stirrer bar and a cooler, ethyl 7-chlorohept-3-enoate **293** (1.3 g, 6.8 mmol, 1 eq) and sodium iodide (5.1 g, 34.0 mmol, 5 eq) were dissolved in acetone. The mixture was stirred at reflux overnight. The reaction was followed by ^{1}H NMR. Diethyl ether was added to the flask: sodium chloride and excess sodium iodide precipitated. The mixture was filtered, concentrated under vacuum and used without further purification.

IR (cm^{-1}) ν_{max} 1732 (C=O). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 1.27 (t, 3H, H-9, *J* 7.0 Hz), 1.90 (quint, 2H, H-6, *J* 7.0 Hz), 2.18 (q, 2H, H-5, *J* 7.0 Hz), 3.13 (dt, 2H, H-3, *J* 7.0 Hz, *J* 0.5 Hz), 3.20 (t, 2H, H-2, *J* 7.0 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 5.48-5.56 (m, 1H, H-4), 5.61-5.69 (m, 1H, H-3). ***m/z*** (ES+) 283 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{16}IO_2^+$) requires ***m/z*** 283.0195, found ***m/z*** 283.0196.

A.6.4. (*Z*)-Ethyl 7-iodohept-3-enoate 291

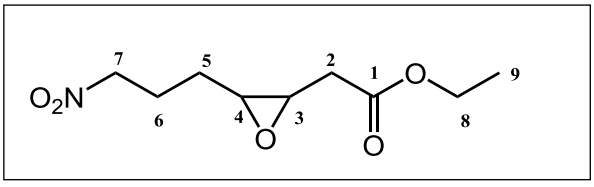


A one-necked flask, equipped with a magnetic stirrer bar, a nitrogen balloon and covered with aluminium foil, was charged with ethyl 7-iodohept-3-eonate **292** (1.0 g, 3.5 mmol, 1 eq) and water. The mixture was cooled to 0 ˚C in an ice / water bath and silver nitrite (2.2 g,14.0 mmol, 4 eq) was added. The mixture was stirred overnight at 0 ˚C and

allowed to warm up to room temperature. The mixture was filtered through celite and washed with ethyl acetate. The water layer was extracted twice with ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum. The purification was achieved by flash column chromatography (petroleum ether / diethyl ether 10:1) to give 0.3 g (40% yield over the 2 steps) of pure product **291**.

IR (cm^{-1}) ν_{max} 1733 (C=O), 1552 (NO_2), 1382 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.26 (t, 3H, H-9, *J* 7.0 Hz), 2.06-2.15 (m, 2H, H-6), 2.15-2.22 (m, 2H, H-5), 3.07 (dd, 2H, H-2, *J* 7.5 Hz, *J* 1.5 Hz), 4.15 (q, 2H, H-8, *J* 7.0 Hz), 4.39 (t, 2H, H-7, *J* 7.0 Hz), 5.50-5.57 (m, 1H, H-4), 5.65-5.72 (m, 1H, H3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.1 (C-9), 24.0 (C-5), 26.8 (C-6), 32.9 (C-2), 60.8 (C-8), 74.7 (C-7), 123.6 (C-3), 130.1 (C-4), 171.5 (C-1). ***m/z*** (ES+) 202 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{16}NO_4^+$) requires ***m/z*** 202.1079, found ***m/z*** 202.1071.

A.6.5. Ethyl [3-(3-nitropropyl)oxiran-2-yl]acetate 289

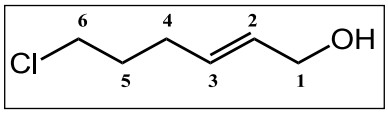


A 100 mL, one-necked flask, equipped with a magnetic stirrer bar and purged with nitrogen, was charged with (*Z*)-Ethyl 7-nitrohept-3-enoate **291** (510 mg, 2.5 mmol, 1 eq), dimethyldioxirane (46 mL, 1.1 eq) and acetone (10 mL). The mixture was stirred at room temperature and the reaction was followed by TLC (petroleum ether / diethyl ether 1:1). Once full conversion was reached, the mixture was reduced under vacuum and purified by flash column chromatography (petroleum ether / diethyl ether 1:1) to give the pure epoxide **289** in 85 % yield.

IR (cm^{-1}) ν_{max} 1733 (C=O), 1552 (NO_2), 1382 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.27 (t, 3H, H-9, *J* 7.0 Hz), 1.46-1.57 (m, 1H, H-5), 1.72-1.80 (m, 1H, H-5'), 2.22 (quint, 2H, H-6, *J* 7.5 Hz), 2.44-2.52 (dd, 1H, H-2, *J* 16.5 Hz, *J* 6.5 Hz), 2.59-2.67 (dd, 1H, H-2', *J* 16.5 Hz, *J* 6.5 Hz), 3.02 (dt, 1H, H-4, *J* 8.0 Hz, *J* 4.5 Hz), 3.34 (td, 1H, H-3, *J* 6.5 Hz, *J* 4.5 Hz), 4.18 (q, 2H, H-8, *J* 7.0 Hz), 4.47 (qt, 2H, H-7, *J* 13.0 Hz, *J* 7.0 Hz), 5.50-5.57 (m, 1H, H-4), 5.65-5.72 (m, 1H, H3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.1 (C-9), 24.4 (C-6), 24.7 (C-5), 33.7 (C-2), 52.4 (C-3), 55.4 (C-4), 61.0 (C-8), 74.8 (C-7), 170.2 (C-1). ***m/z*** (ES+) 240 ($[M+Na]^+$, 100%).

A.7 Experimental- Chapter 7

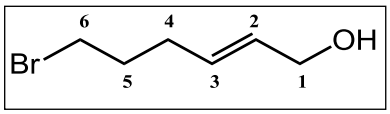
A.7.1. (2*E*)-6-chlorohex-2-en-1-ol 321



A one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with ethyl (2*E*)-6-chlorohex-2-enoate (1.7 g, 9.7 mmol, 1 eq) and dry diethyl ether (9.0 mL, 1 mol/L). The reaction was cooled to 0 ˚C and a 1 M solution of DIBAL-H in hexane (27.6 mL, 27.6 mmol, 3 eq) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 2 hours. It was then cooled to 0 ˚C and quenched with 1M aqueous HCl. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether / diethyl ether 2:1, R_f = 0.4). (2*E*)-6-chlorohex-2-en-1-ol **321** was isolated in 85% yield (1.0 g) as a colourless oil.

IR ν_{max} (cm^{-1}) 3230-3420 (OH), 970 (C=C-H), 651 (C-Cl).**^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.46 (br s, 1H, OH), 1.81-1.97 (m, 2H, H-5), 2.15-2.29 (m, 2H, H-4), 3.55 (t, 2H, H-6, *J* 6.5 Hz), 4.11 (dd, 2H, H-1, *J* 3.5 Hz, *J* 1.0 Hz), 5.49-5.79 (m, 2H, H-2 and H-3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 29.2 (C-5), 31.8 (C-4), 44.3 (C-6), 63.5 (C-1), 130.4 (C-3), 130.9 (C-2). ***m/z*** HRMS (TOF MS FI+) exact mass calculated for ($[M]^+$) ($C_6H_{11}OCl^+$) 134.0498.

A.7.2. (2*E*)-6-bromohex-2-en-1-ol 328

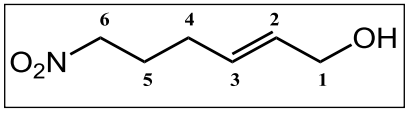


A one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with ethyl (2*E*)-6-bromohex-2-enoate (1.2 g, 5.4 mmol, 1 eq) and dry diethyl ether (5.0 mL, 1 mol/L). The reaction was cooled to 0 ˚C and a 1 M solution of DIBAL-H in hexane (15.8 mL, 15.8 mmol, 3 eq) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 2 hours. It was then cooled to 0 ˚C and quenched with 1M aqueous HCl. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography

(petroleum ether / diethyl ether 2:1, R_f = 0.4). (2*E*)-6-bromohex-2-en-1-ol **328** was isolated in 85% yield (0.8 g) as a colourless oil as a 1:1 mixture of bromide and chloride analogue. The data collected matched those of the literature.[112]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 1.35 (br s, 1H, OH), 1.82-2.04 (m, 2H, H-5), 2.16-2.30 (m, 2H, H-4), 3.42 (t, 1H, H-6 (C-Br), *J* 6.5 Hz), 3.55 (t, 1H, H-6 (C-Cl), *J* 6.5 Hz), 4.02-4.21 (m, 2H, H-1), 5.63-5.75 (m, 2H, H-3 and H-2). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 26.6 (C-5), 28.7 (C-4), 63.2 (C-1), 74.8 (C-6), 129.4 (C-3), 131.3 (C-2). ***m/z*** (TOF MS FI+) 177 ($[M]^+$, 100%).

A.7.3. (2*E*)-6-nitrohex-2-en-1-ol 322

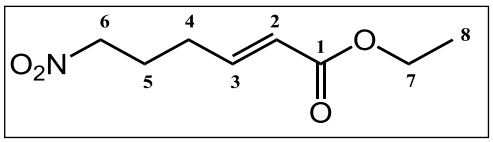


A one-necked flask, equipped with a rubber seal, a magnetic stirrer bar and a condenser, was charged with (2*E*)-6-bromohex-2-en-1-ol **328** (1.2 g, 6.7 mmol, 1 eq), sodium iodide (5.0 g, 33.5 mmol, 5 eq) and acetone (50 mL, 0.15 mol/L). The flask was covered in aluminium flask and the reaction was heated to reflux and stirred overnight. Diethyl ether was added and the inorganic salts were filtered through cotton. The solvent was removed under vacuum and (2*E*)-6-iodohex-2-en-1-ol was used without further purification. It was taken up in water (25 mL) in a one-necked flask covered in aluminium foil. The mixture was cooled to 0 ˚C and silver nitrite (5.1 g, 26.8 mmol, 4 eq) was added. The suspension was allowed to warm up to room temperature and stirred for 48 hours. The aqueous layer was then extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether / diethyl ether 1:1, R_f = 0.4). (2*E*)-6-nitrohex-2-en-1-ol **322** was isolated in 47% yield (0.6 g) over the two steps as a colourless oil.

IR (cm^{-1}) ν_{max} 3320-3380 (OH), 1548 (NO_2), 1383 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.63 (br s, 1H, OH), 2.08-2.15 (m, 2H, H-5), 2.15-2.22 (m, 2H, H-4), 4.11 (dd, 2H, H-1, *J* 5.5 Hz, *J* 1.0 Hz), 4.39 (t, 2H, H-6, *J* 7.0 Hz), 5.49-5.91 (m, 2H, H-2 and H-3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 26.5 (C-5), 28.7 (C-4), 63.2 (C-1), 74.8 (C-6), 129.4 (C-3), 131.3 (C-2). ***m/z*** (ES+) 168 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_6H_{11}NO_3Na^+$) requires ***m/z*** 168.0631, found ***m/z*** 168.0636.

[112] Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112-1124.

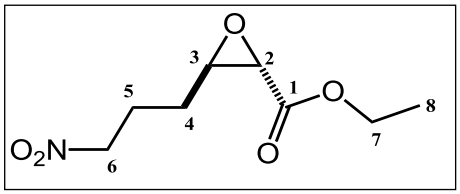
A.7.4. Ethyl (2*E*)-6-nitrohex-2-enoate 329



A one-necked flask, equipped with a rubber seal, a magnetic stirrer bar and a condenser, was charged with ethyl (2*E*)-6-bromohex-2-enoate (2.0 g, 9.1 mmol, 1 eq), sodium iodide (6.8 g, 45.5 mmol, 5 eq) and acetone (25 mL, 0.15 mol/L). The flask was covered in aluminium foil and the reaction was heated to reflux and stirred overnight. Diethyl ether was added and the insoluble inorganic salts were filtered through cotton. The solvent was removed under vacuum and ethyl (2*E*)-6-iodohex-2-enoate (1 eq) was used without further purification. It was taken up in water (25 mL) in a one-necked flask covered in aluminium foil. The mixture was cooled to 0 ˚C and silver nitrite (7.0 g, 36.4 mmol, 4 eq) was added. The suspension was allowed to warm up to room temperature and stirred for 48 hours. The aqueous layer was then extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether / diethyl ether 2:1, R_f = 0.35). Ethyl (2*E*)-6-nitrohex-2-enoate **329** was isolated in 42% yield (0.7 g) over the two steps as a colourless oil.

IR (cm^{-1}) ν_{max} 1715 (C=O), 1551 (NO_2), 1370 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.30 (t, 3H, H-8, *J* 7.0 Hz), 2.20 (quint, 2H, H-5, *J* 7.0 Hz), 2.29-2.45 (m, 2H, H-4), 4.20 (q, 2H, H-7, *J* 7.0 Hz), 4.41 (t, 2H, H-6, *J* 7.0 Hz), 5.89 (dt, 1H, H-2, *J* 15.5 Hz, *J* 1.5 Hz), 6.90 (dt, 1H, H-3, *J* 15.5 Hz, *J* 7.0 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.2 (C-8), 25.6 (C-5), 28.5 (C-4), 60.4 (C-7), 74.4 (C-6), 123.3 (C-2), 145.3 (C-3), 166.1 (C-1). ***m/z*** (ES+) 210 ([M+Na]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_8H_{13}NO_4Na^+$) requires ***m/z*** 210.0737, found ***m/z*** 210.0741.

A.7.5. Ethyl 2,3-anhydro-4,5,6-trideoxy-6-nitrohexonate 330

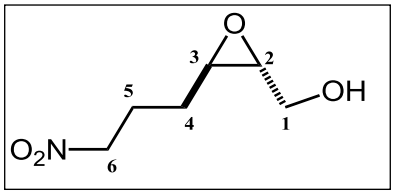


A one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with ethyl (2*E*)-6-nitrohex-2-enoate **329** (0.7 g, 3.7 mmol, 1.0 eq), *m*-CPBA (1.3 g, 5.6 mmol, 1.5 eq) and dichloromethane (0.4 mol/L). The mixture was stirred at room temperature overnight. Sodium sulphite was added portionwise to quench the excess peroxide, then

dichloromethane was removed under vacuum. The crude material was purified by flash column chromatography (petroleum ether / ethyl acetate 1:1, then pure ethyl acetate, R_f (ethyl acetate = 0.5). Ethyl 2,3-anhydro-4,5,6-trideoxy-6-nitrohexoate **330** was isolated in 81% yield (0.6 g) as a colourless oil.

IR (cm^{-1}) ν_{max} 1742 (C=O), 1552 (NO_2), 1375 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.31 (t, 3H, H-8, *J* 7.5 Hz), 1.58 (dq, 1H, H-4, *J* 14.5 Hz, *J* 7.5 Hz), 1.95 (dtd, 1H, H-4', *J* 14.5 Hz, *J* 7.5 Hz, *J* 4.0 Hz), 2.21 (quint, 2H, H-5, *J* 7.5 Hz), 3.21 (ddd, 1H, H-3, *J* 7.5 Hz, *J* 4.0 Hz, *J* 2.0 Hz), 3.26 (d, 1H, H-2, *J* 2.0 Hz), 4.18-4.33 (m, 2H, H-7), 4.40-4.56 (m, 2H, H-6). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.1 (C-8), 23.7 (C-5), 28.1 (C-4), 52.7 (C-2), 56.9 (C-3), 61.8 (C-7), 74.6 (C-6), 168.6 (C-1). ***m/z*** (ES+) 226 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{13}NO_5Na^+$) requires ***m/z*** 226.0686, found ***m/z*** 226.0689.

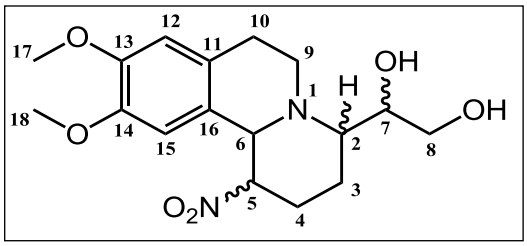
A.7.6. 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitol 323



A one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with (2*E*)-6-nitrohex-2-en-1-ol **322** (0.8 g, 5.5 mmol, 1.0 eq), *m*-CPBA (1.5 g, 8.3 mmol, 1.5 eq) and dichloromethane (0.4 mol/L). The mixture was stirred at room temperature overnight. Sodium sulphite was added portionwise to quench the excess peroxide, then dichloromethane was removed under vacuum. The crude material was purified by flash column chromatography (petroleum ether / ethyl acetate 1:1, then pure ethyl acetate), R_f = 0.4 (ethyl acetate). 4,5-Anhydro-1,2,3-trideoxy-1-nitrohexitol **323** was isolated in 70% yield (0.6 g) as a colourless oil.

IR (cm^{-1}) ν_{max} 3200-3500 (OH), 1549 (NO_2), 1384 (NO_2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.57 (dq, 1H, H-4, *J* 14.5 Hz, *J* 7.0 Hz), 1.80-1.89 (m, 1H, H-4'), 1.95 (br s, 1H, OH), 2.19 (quint, 2H, H-5, *J* 7.0 Hz), 2.93-2.97 (m, 1H, H-2), 3.02 (ddd, 1H, H-3, *J* 7.0 Hz, *J* 4.0 Hz, *J* 2.0 Hz), 3.66 (dd, 1H, H-1, *J* 12.5 Hz, *J* 4.0 Hz), 3.91 (dd, 1H, H-1', *J* 12.5 Hz, *J* 2.5 Hz), 4.41-4.52 (m, 2H, H-6). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 24.0 (C-5), 28.2 (C-4), 54.5 (C-3), 58.1 (C-2), 61.2 (C-1), 74.9 (C-6). ***m/z*** (ES+) 184 ($[M+Na]^+$, 100%), HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_6H_{11}NO_4Na^+$) requires ***m/z*** 184.0580, found ***m/z*** 184.0585.

A.7.7. 1-(9,10-dimethoxy-1-nitro-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-4-yl)ethane-1,2-diol 332



A one-necked flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with 4,5-anhydro-1,2,3-trideoxy-1-nitrohexitol **323** (25 mg, 0.15 mmol, 1.0 eq), 6,7-dimethoxy-3,4-dihydroisoquinoline **176c** (42 mg, 0.22 mmol, 1.5 eq) and methanol (0.4 mol/L). The mixture was stirred at 55 °C overnight. Methanol was removed under vacuum and the crude material was purified by flash column chromatography (petroleum ether / ethyl acetate 2:1, R_{f1}=0.3 and R_{f2}=0.1) to give18 mg two unseparable diastereoisomers of 1-(9,10-dimethoxy-1-nitro-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-4-yl)ethane-1,2-diol **332** were isolated.

Data for the mixture of diastereoisomers a and b.

IR (cm^{-1}) ν_{max} 3200-3500 (OH), 1612 (C=C aromatic), 1543 (NO_2), 1520 (NO_2), 1464 (C=C aromatic), 1375 (NO_2), 1341 (NO_2), 1246 (C-O aromatic), 1229 (C-O aromatic). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 1.65 (br s, 2H, OH), 1.69-1.81 (m, 1H, H-3a), 1.92 (tt, 1H, H-3b, *J* 14.0 Hz, *J* 4.5 Hz), 1.99-2.07 (m, 1H, H-3'a), 2.10-2.19 (m, 1H, H-3'b), 2.23 (dq, 1H, H-4a, *J* 13.0 Hz, *J* 4.0 Hz), 2.32-2.50 (m, 2H, H-4b), 2.50-2.59 (m, 2H, H-4'a), 2.68-2.77 (m, 2H, H-10a), 2.84-3.07 (m, 5H, H-2a, H-2b, H-9a, H-9b), 3.34 (td, 1H, H-9'a, *J* 11.5 Hz, *J* 4.0 Hz), 3.68-3.92 (m, 17H, H-7a, H-8a, H-8b, H-17a, H-17b, H-18a and H-18b), 4.23 (d, 1H, H-**194a**, *J* 10.0 Hz), 4.24-4.32 (m, 1H, H-7'b), 4.37 (d, 1H, H-6'a, *J* 10.0 Hz), 4.78-4.94 (m, 2H, H-5a and H-5b), 6.32 (s, 2H, H-15a and H-15b), 6.59 (s, 1H, H-12a), 6.60 (s, 1H, H-12b).**^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 17.9 (C-3a), 19.5 (C-3b), 26.5 (C-4a), 28.5 (C-10a), 28.9 (C-10b), 30.9 (C-4b), 38.6 (C-9b), 47.0 (C-9a), 55.7 (C-17a and C-17b), 55.8 (C-18a and C-18b), 55.2 (C-**194a**), 63.1 (C-6b), 63.9 (C-2a), 64.1 (C-2b), 65.4 (C-8a), 66.7 (C-8b), 67.3 (C-7a), 71.7 (C-7b), 85.2 (C-5a and C-5b), 109.6 (C-15), 109.8 (C-15b), 111.4 (C-12), 111.5 (C-12b), 124.3 (C-1**194a** or C-16b or C-11a or C-11b), 125.2 (C-1**194a** or C-16b or C-11a or C-11b), 125.6 (C-1**194a** or C-16b or C-11a or C-11b), 125.7 (C-1**194a** or C-16b or C-11a or C-11b), 147.1 (C-13a or C-13b or C-14a or C-14b), 147.2 (C-13a or C-13b or C-14a or C-14b), 148.7 (C-13a or C-13b or C-14a or C-14b), 147.8 (C-13a or C-13b or C-14a or C-14b). ***m/z*** (ES+) 353

([M+H]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+H]$^+$ ($C_{17}H_{25}N_2O_6^+$) requires ***m/z*** 353.1707, found ***m/z*** 353.1706.

Appendix B

List of Acronyms

˚C	degree Celsius
Å	angstrom
δ	chemical shift
v	absorbance
µL	microliter
Ac	acetyl
AIBN	2,2’-azoisobutyronitrile
Ar	aryl
Atm	atmosphere
BINAP	2,2’-bis(diphenylphosphino)-1’1’-binaphthyle
BINOL	1,1’-bi-2-napthol
BMS	borane dimethylsulfide
Bn	benzyl
Boc	*tert*-butylcarbonyl
BOX	*bis*-oxazoline
br	broad
Bu	butyl
c	concentration
c	*cyclo*
CAN	ceric ammonium nitrate
Cby	carbamoyl
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminiumhydride
DMF	dimethylformamide

DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMPU	*N*,*N*'-dimethyl-*N*,*N*'-propylene urea
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dt	doublet of triplet
ee	enantiomeric excess
EI	electron impact
eq	equivalent
ESI	electron spray ionisation
Et	ethyl
EtOH	ethanol
g	gram
(g)	gas
h	hour
Hex	hexyl
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
i or ^{i}	*iso*
IR	infrared spectroscopy
J	coupling constant
K	kelvin
KHMDS	potassium hexamethyldisilazide (potassium *bis*(trimethylsilyl) amide
L	litre
LDA	lithium diisopropylamide

m	multiplet
m	*meta*
M	molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute
mL	milliliter
mol	mole
mp	melting point
Ms	mesyl
MS	molecular sieves
m/z	mass-to-charge ratio
n or ^{n}	*normal*
NCS	*N*-chlorosuccinimide
NME	*N*-methylephedrine
NMR	nuclear magnetic resonance
o	ortho
OMP	*ortho*-methoxyphenyl
P or Pet	petroluem
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
Pn	pentyl
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl

psi	pound per square inch
*p*TSA	*para*-toluenesulfonic acid
q	quartet
quat	quaternary
quint	quintet
rac	racemic
Ra-Ni	Raney®-nickel
R_f	retention factor
RT	room temperature
s	singlet
sept	septuplet
septd	septuplet of doublet
sext	sextuplet
t	triplet
t or ^{t}	*tert*
TBAF	tetra-*n*-butylammonium fluroride
TBS	*tert*-butyldimethylsilyl
td	triplet of doublet
Temp	temperature
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
wt	weight

Nitro-Mannich Reaction Cascades: New Methods and Synthetic Applications

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DPhil organic chemistry, Michaelmas 2011

Pyrrolidine and pyrrolidinone rings are common motifs found in many biologically active natural products and drugs. Accordingly, our work focuses on the development of new methodologies for their one-pot synthesis.

An efficient diastereoselective nitro-Mannich / lactamisation reaction cascade of methyl 3-nitropropanoate with cyclic and acyclic imines for the direct preparation of *trans*-monocyclic and fused tricyclic pyrrolidinone derivatives was developed. The reaction is easy to perform, broad in scope and tolerates a wide variety of functional groups. For the monocyclic methodology, 28 examples with a very good average yield of 72% and excellent diastereocontrol (typical dr >98:2) were obtained using optimized conditions and varying the amine and the aldehyde reagents.

The methodology has been extended to the synthesis of 1,3,5-trisubstituted 4-nitropyrrolidinone derivatives using α-substituted 3-nitropropanoate. Using a one-pot protocol, 22 derivatives were synthesised in good yields (65% average) and diastereomeric ratios ranging from 3:1 to 30:1 in favor of the *trans/trans* diastereoisomer.

In addition, the nitro-Mannich / lactamisation cascade of methyl 3-nitropropanoate was developed further to allow the rapid synthesis of 5-isopropyl-4-nitropyrrolidin-2-one from reaction with ammonium acetate and 1-butyl-4-nitropyrrolidin-2-one from reaction with formaldehyde. Also, the synthetic utility of the nitro-pyrrolidinones formed was exemplified through various functional group modifications: the selective reduction of the lactam carbonyl, the reduction of the nitro group in the presence or absence of a carbonyl group and the reductive removal of the nitro group.

The development of an enantioselective version of the cascade under chiral Brönsted acid catalysis provided promising results (up to 90% ee).

Moreover, various studies were undertaken to understand the mechanism of the reaction and the nitro-Mannich / latamisation cascade is now well understood.

Furthermore, a formal synthesis of *rac*-Slaframine in 8 steps and 15% overall yield was achieved and it inspired additional work towards a nitro-Mannich / epoxide ring opening cascade.